

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

TWINSTRAND BIOSCIENCES, INC. &
UNIVERSITY OF WASHINGTON,

Plaintiffs,

v.

GUARDANT HEALTH, INC.,

Defendant.

C.A. No. 21-1126-GBW-SRF

JOINT CLAIM CONSTRUCTION BRIEF

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I. Introduction

A. Plaintiffs' Opening Introduction

This suit involves patent-infringement claims and counterclaims on two sets of patents, one set asserted by Plaintiffs TwinStrand Biosciences, Inc. and the University of Washington,¹ the other asserted by Defendant Guardant Health, Inc.² Although Plaintiffs' patents have priority dates that are nearly two years before Guardant's patents' priority dates, all of the patents-in-suit are directed to similar methods of error-correcting DNA sequencing. Plaintiffs' claimed inventions, including Duplex Sequencing methods, lower the error rate for next-generation sequencing (NGS) platforms, allowing researchers and clinicians to identify a genetic needle in a haystack by differentiating true genetic mutations from sequence errors that occur during the sequencing work flow.

The claim-construction disputes here fall within six categories, five involving terms in Plaintiffs' patents and one involving terms in Guardant's patents. As shown below, Plaintiffs' proposed constructions (where construction is even necessary) are supported by the plain language of the claims themselves, the intrinsic record of the patents, and by the extrinsic evidence. In contrast, Guardant's proposed constructions are litigation-driven and generally attempt to read limitations from the specifications into the claims, contrary to settled principles of law. The Court should adopt Plaintiffs' proposed constructions of the disputed terms.

¹ Plaintiffs' asserted patents are U.S. Patent Nos. 10,287,631 ('631 patent); 10,689,699 ('699 patent); 10,752,951 ('951 patent); and 10,760,127 ('127 patent). All four patents are related by priority and, in all relevant respects here, share an identical specification.

² Guardant's asserted patents are U.S. Patent Nos. 10,801,063 ('063 patent); 10,889,858 ('858 patent); 11,118,221 ('221 patent); and 11,149,306 ('306 patent).

B. Plaintiffs' Opening Background

1. Plaintiffs' Patents and Duplex Sequencing Technology

The invention of Duplex Sequencing dates to 2011, when Jesse Salk, Michael Schmitt, and Lawrence A. Loeb, then of the University of Washington, invented a new method of correcting errors in NGS that allowed researchers to identify DNA variants that are present at extremely low frequencies. At that time, NGS sequencing offered high-throughput, low-cost sequencing, but was notoriously inaccurate, generating error rates of 0.1%–1%. This meant that up to one in one hundred DNA bases were miscalled and true biological mutations were obscured by the noisy, error-filled sequence data. For this reason, conventional NGS methods could not be used effectively in certain applications. For example, where the variant DNA occurs at a low frequency in a sample, such as with cancer DNA biomarkers in blood, these DNA variants were impossible to detect given the noisy data produced by conventional NGS methods. The inventions of Plaintiffs' patents overcome the shortcomings of conventional NGS methods, offering unprecedented accuracy and specificity without sacrificing the high throughput of modern DNA-sequencing approaches. And they accomplish this by several strategies—chief among them—by leveraging the reciprocal information stored in each complementary strand of DNA, also known as Duplex Sequencing.

Plaintiffs' patents claim methods of error-correcting DNA sequencing, including Duplex Sequencing. Each of these methods include steps whereby a population of DNA molecules are tagged with (or affixed to) molecular barcodes. These barcodes endow the affixed-DNA molecules with information that helps distinguish an individual molecule from other molecules in the same sample. The barcodes, alone or together with other information, are then used to separately track each strand of sequenced DNA and relate sequence reads from each strand back to its original template molecule.

The ability to track and relate individual, complementary strands (*i.e.*, the top and bottom strands) of a target molecule to one another is important because true mutations are confirmed by being present in both complementary strands, whereas a sequencing error at a given position essentially only ever occurs on one strand. Other NGS approaches were unable to distinguish between true mutations and sequencing errors because they relied “on interrogating single-stranded DNA.” Ex. 1 (’631 patent) at 16:64–65. By comparing information from the top and bottom strands of the DNA, Duplex Sequencing identifies true mutations and eliminates the sequencing errors. *Id.* at 17:12–16. Indeed, in at least one instance, Duplex Sequencing “represents a greater than 3 million fold improvement over the error rate ... that was obtained by a standard sequencing approach.” *Id.* at 28:48–51.

2. Guardant’s Patents

Guardant’s patents also claim methods of error correcting DNA sequencing for NGS applications. Indeed, Guardant’s patents add little more than trivial variations on Plaintiffs’ earlier inventions. There is only one basic claim-construction dispute involving Guardant’s patents. And it centers purely on the meaning of “comprising.” *See* Section III.B.1. Accordingly, this dispute does not present any technical or scientific issue for the Court to delve into but only requires it to apply well-settled legal customs and rules.

C. Defendant’s Answering Introduction

Guardant’s mission is to conquer cancer with data. Guardant’s FDA-approved and patented innovations revolutionized the use of blood tests to detect early-stage cancer when it is the most treatable, and Guardant’s growing data sets are used to inform the treatment of patients with advanced cancer. Guardant’s proposed claim constructions are true to its patented inventions and are well-supported by both intrinsic and extrinsic evidence.

Founded in 2012, Guardant successfully developed groundbreaking liquid biopsy

technology to sequence cell-free DNA (“cfDNA”) from blood drawn from patients to identify cancer-causing mutations. Guardant was the first to use cfDNA to detect such mutations and this new approach provided substantial advantages over prior cancer detection techniques, which relied upon invasive tissue biopsies that were painful, slower, costly and sometimes less accurate. Guardant’s innovations resulted in its 2014 commercial release of Guardant360—the world’s first commercial liquid biopsy assay used to detect mutations in cfDNA to identify cancer. Over the ensuing years, Guardant has continued to innovate and release blood test products to detect and provide critically important data regarding early and late-stage cancers.

Guardant’s products reflect the pioneering inventions claimed in its patents.³ In addition to the groundbreaking use of cfDNA to detect cancer-causing mutations, Guardant’s claimed inventions also introduced the use of non-unique tags in its sequencing methods, which generally are directed to: (1) collecting a bodily fluid sample from a patient; (2) extracting and isolating double-stranded DNA, including cfDNA, from the sample; (3) tagging the double-stranded DNA with an adapter/barcode in which the Watson strand tag is distinguishable from the Crick strand tag; (4) amplifying the tagged DNA; (5) sequencing the amplified DNA to produce sequence reads; and (6) identifying true mutations in the sequence reads. *See, e.g.*, Ex. 7, ’221 patent at FIG. 1.

Unlike Guardant, TwinStrand is not an innovator—not in the lab, not in the market, and not in its patents. TwinStrand has no FDA-approved products and has not successfully commercialized anything. And, reflecting the fact that it is Guardant, not TwinStrand, that is the true innovator, Plaintiffs’ patent specifications do not expressly describe using either cfDNA or

³ Guardant’s asserted patents are U.S. Patent Nos. 10,801,063 (“’063 patent”) (Ex. 5), 10,889,858 (“’858 patent”) (Ex.6), 11,118,221 (“’221 patent”) (Ex. 7), and 11,149,306 (“’306 patent”) (Ex. 8).

non-unique tags, and the patents include no examples of using non-unique tags to analyze cfDNA, all of which was developed first by Guardant. Recognizing that it was trailing Guardant in this regard, Plaintiffs took the improper shortcut of copying claims from Guardant patent applications into Plaintiffs' patents without notifying the Patent Office. *See* D.I. 30 (Guardant's Amended Answer and Counterclaims) at ¶¶ 125, 140-148, 246-269. Continuing down the path of taking shortcuts rather than innovating, TwinStrand's current claim construction positions improperly seek to broaden its alleged inventions beyond what actually is described in its patents in attempting to cover Guardant's revolutionary technology.

The TwinStrand asserted patent specifications describe methods to detect genetic variations in DNA sequences using unique (rather than non-unique) tagging.⁴ And further unlike Guardant's technology, three of TwinStrand's asserted patents—the '631, '951 and '127 patents—require using molecular tags in which all or some of the nucleotides have been randomly generated (*i.e.*, degenerate or semi-degenerate tags). Plaintiffs' fourth asserted patent, the '699 patent, does not claim the use of such tags, which is unsurprising because Plaintiffs copied claims from a pending Guardant patent application into their own application during prosecution of that patent. As shown below, however, the claims of the '699 patent—as well as several claims of the '951 and '127 patents where TwinStrand also attempted to stretch its claimed invention beyond what it described in its patent specifications—are invalid because they are indefinite.

D. Plaintiffs' Reply Introduction

Guardant's attempt to portray itself as a pioneer and Plaintiffs as copyists in the field of

⁴ TwinStrand's asserted patents are U.S. Patent Nos. 10,287,631 ("'631 patent") (Ex. 1), 10,689,699 ("'699 patent") (Ex. 2), 10,752,951 ("'951 patent") (Ex. 3) and 10,760,127 ("'127 patent") (Ex. 4).

duplex sequencing is irrelevant to the claim-construction issues in this case and does not square with the facts. In fact, it is Guardant who has been profiting off the ideas and inventions of others for almost a decade, a pattern that is supported by multiple third-party lawsuits.

Twinstrand’s patents pre-date Guardant’s: Skilled artisans had long sought to reduce the error rate in sequencing to improve the detection of true mutations. And, there is no dispute that the core invention disclosed in Plaintiffs’ patents—the invention of separately tracking and matching the top and bottom strands to identify true mutations—was not in the prior art to Plaintiffs’ patents. Plaintiffs filed their provisional application in March 2012, a year and a half before Guardant filed its first provisional application on its countersuit patents. The inventors of Plaintiffs’ patents, after filing their provisional patent applications, published several papers on their invention and presented their findings at conferences. Guardant, meanwhile, after learning of Plaintiffs’ inventions, attempted but failed to license the patents from the University of Washington and to hire one of TwinStrand’s co-founders. Guardant nevertheless proceeded to incorporate Plaintiffs’ inventions into its own patents and its infringing products.

Guardant’s pattern of stealing ideas is not limited to Plaintiffs’ inventions. In March 2022, another entity, Illumina, sued Guardant and its founders, accusing its founders—who are also named inventors on Guardant’s countersuit patents—of stealing Illumina’s trade secrets and incorporating them into Guardant’s intellectual property and products. *See Illumina, Inc. v. Guardant Health, Inc., Helmy Eltoukhy, and AmirAli Talasaz*, C.A. No. 1:22-cv-00334-GBW-CJB (D. Del.). In an earlier lawsuit on patents related to Guardant’s countersuit patents, Guardant’s co-founder—accused of inequitable conduct because he had intentionally omitted himself as an inventor on Guardant patents to avoid the fact that he was employed at Illumina while working on these inventions—was found by a court in this District to have deleted

hundreds of documents in his possession. *See* Ex. 46, *Guardant Health, Inc. v. Foundation Medicine, Inc.*, No. 1:17-cv-1616-LPS-CJB, D.I. 289 (Oral Order), Ex. 47, D.I. 517 (Memorandum Order) (D. Del.). That lawsuit settled on the day of the hearing on a spoliation motion related to these actions. *Id.* at D.I. 553 (Oral Order).

Guardant’s copying claims: Setting aside that Guardant’s claim-copying allegations are the subject of a Motion to Dismiss by Plaintiffs (D.I. 39), Guardant’s claims are factually and legally unsupported. Guardant alleges that Plaintiffs copied claims from Guardant’s ’822 patent into the patent application that issued as Plaintiffs’ ’699 patent. But, a simple comparison of the ’699 patent application claims and the ’822 patent shows that the claims have different claim scopes. Most notably, the ’699 patent application claims were directed to “circulating DNA” while Guardant’s ’822 patent claims recite “cell free DNA,” and as Guardant has agreed in its claim construction brief (at 8–9), the scope of the terms “circulating DNA” and “cell-free DNA” are different. And, Guardant’s copying allegation for Plaintiffs’ ’951 patent is unsustainable under the very statute that Guardant alleges copying—the priority application for the ’951 patent *predates* the Guardant application that Guardant alleges Plaintiffs’ copied. *See* 35 U.S.C. § 135(b). Guardant’s copying allegations serve only as a smokescreen to its own misdeeds.

E. Defendants’ Sur-reply Introduction

Plaintiffs’ proposed constructions are litigation driven and untethered from a POSA’s understanding, as evidenced by testimony of Plaintiffs’ expert, Dr. Ehrlich, that he did not have input into Plaintiffs’ proposed constructions. Ex. 48, Ehrlich Tr. 11:14-18. Indeed, Dr. Ehrlich’s recent deposition testimony undermines many of Plaintiffs’ positions. Instead of engaging with the most compelling claim construction arguments, Plaintiffs obfuscate the issues, advancing a misleading timeline of their alleged inventions and interactions with Guardant, citing unrelated lawsuits, and misrepresenting Guardant’s claim copying arguments. Plaintiffs presumably rely

on this false narrative to distract from their faulty claim construction positions that fail to comport with the intrinsic and extrinsic evidence.

II. Agreed-Upon Constructions

The parties have agreed to the construction of several terms in their respective patents, which are set forth in the tables provided below.

A. Agreed-upon Terms in Plaintiffs' Patents

Claim Term	Patent, Claim	Agreed Upon Construction
"uniquely labels"	'631 patent, claim 1	Plain and ordinary meaning
"quantifying at least two of (i) said paired sequence reads, (ii) said unpaired sequence reads, (iii) read depth of said paired sequence reads, and (iv) read depth of said unpaired sequence reads"	'951 patent, claim 1	Plain and ordinary meaning
"partially single-stranded adapters"	'127 patent, claim 22	Plain and ordinary meaning with the understanding that the term can include both Y-shaped and U-shaped adaptors
"partially complementary, asymmetrical double-stranded adapter-DNA molecules"	'127 patent, claim 1	Plain and ordinary meaning with the understanding that the term can include both Y-shaped and U-shaped adaptors
"other fragment regions"	'631 patent, claim 18	Plain and ordinary meaning
"circulating DNA molecule(s)"	'699 patent, claims 1, 8, 9, 12, 17–20, 24, 25	DNA molecules that circulate within the circulatory system, which can include cell-free DNA and cellular DNA
"double-stranded circulating nucleic acid molecules"	'951 patent, claims 11, 12, 15, 16, 18	Double-stranded nucleic acid molecules that circulate within the circulatory system, which can include cell-free DNA and cellular DNA

B. Agreed-upon Terms in Defendants' Patents

Claim Term	Patent, Claim	Agreed Upon Construction
"cell-free deoxyribonucleic acid (cfDNA)"	'063 patent, claims 15 and 24 '858 patent, claims 1, 3, and 5 '221 patent, claims 1–5 '306 patent, claims 17, 19, and 20	"DNA that exist(s) outside of a cell while in the body, including in blood, plasma, serum, urine, saliva, mucosal excretions, sputum, stool, cerebral spinal fluid, or tears."
"a family of the families"	'063 patent, claim 17	"a single family from the plurality of families"
"a subject having cancer"	'221 patent, claim 2	Plain and ordinary meaning

C. Terms No Longer Requiring Construction

Because Plaintiffs are no longer asserting certain patent claims, the need to construe the following terms has been mooted:

- "non-unique polynucleotide barcode";
- "non-uniquely tagged double stranded adapter-DNA molecules";
- "substantially identifiable"; and
- "sufficiently unique...substantially differentiated."

III. Disputed Constructions**A. Disputed Terms in Plaintiffs' Patents****1. The "non-unique" terms**

Claim Term	Patent, Claim	Plaintiffs' Proposed Construction	Defendant's Proposed Construction
"non-uniquely tagged parent polynucleotide(s)"	'699 patent, claims 1, 18;	a population of parent polynucleotide molecules affixed to polynucleotide	Indefinite

		barcodes, wherein the same polynucleotide barcode sequence is affixed to multiple parent polynucleotide molecules in the [population/sample], and wherein the polynucleotide barcode sequence serves as a molecular identifier only when combined with other information from the tagged parent polynucleotide molecule	
“non-unique tag”	’951 patent, claim 25	a tag that is affixed to a parent polynucleotide molecule and having a nucleotide sequence, wherein the same tag nucleotide sequence is affixed to multiple parent polynucleotide molecules in the sample, and wherein the tag nucleotide sequence serves as a molecular identifier only when combined with other information from the tagged parent polynucleotide molecule	Indefinite
“substantially unique”	’699 patent, claims 1, 20	Plain and ordinary meaning; not indefinite	Indefinite

(a) Plaintiffs’ Opening Position⁵

Broadly speaking, the patents claim two types of tags: “unique tags” and “non-unique tags.” In the claims, tags (which are themselves comprised of nucleotide sequences) are attached to parent polynucleotide molecules and used to identify those molecules in the claimed methods.

⁵ Guardant does not propose constructions for these terms; instead, it wrongly alleges that each of them is indefinite. Plaintiffs disagree and will address Guardant’s indefiniteness arguments for these terms, and their indefiniteness arguments for other terms, in their reply brief.

It is these tags' own nucleotide sequence that allows them to serve this function: different tags will have different nucleotide sequences, allowing one to distinguish among different tags. The parties' dispute here centers on the meaning of "non-unique" in its various forms—not on the meaning of "unique" or the connected terms "tag" or "tagged."

The term "non-unique," like its counterpart "unique," is not particularly technical, nor is its meaning in any way obscure. A "non-unique" tag is just as it sounds, a tag that has a nucleotide sequence that is identical to other tags that are attached to multiple parent polynucleotide molecules in the same sample.⁶ Plaintiffs' proposed constructions do not deviate from this common parlance; to the contrary, they embody it.

To understand how the specifications describe the use of "non-unique tags" in the claimed inventions, it is useful to begin with a comparison to the patents' description of "unique tags." The specifications describe multiple Duplex Sequencing methods that use "unique tags." *See, e.g.*, Ex. 2 ('699 patent) at 3:52–4:37, 19:57–25:6; Ex. 3 ('951 patent) at 3:52–4:37, 19:19–24:32; Ex. 4 ('127 patent) at 3:52–4:37, 19:9–24:24. Like "non-unique tags," these "unique tags" are just as the term suggests; they are tags that are distinct from one another, with no two of the same tag nucleotide sequence being attached to multiple parent polynucleotide molecules, except in extremely rare instances. Ehrlich Decl. (Ex. 9), ¶ 46 (citing Ex. 2 at 3:56–59); *see also, e.g.*, Ex. 2 at 6:67–7:13; Ex. 3 at 6:67–7:13; Ex. 4 at 6:67–7:13. Because of this, methods using unique tags rely solely on the information on the tags to precisely (*i.e.*, uniquely) identify individual parent polynucleotide molecules. Ehrlich Decl., ¶ 44. Plaintiffs' patents cite examples

⁶ As will be explained below, the patented methods combine the information in the non-unique tags with other information from the tagged parent polynucleotide to allow for precise (or unique) identification of the various parent polynucleotide molecules. Non-unique tags can only serve as precise (unique) identifiers when they are combined with this additional information. *See* Section III.A.1(a).

of unique tags from the prior art. For example, Miner⁷ reports tagging a population of polynucleotide molecules with a highly diverse set of tags, such that the probability of two genomic fragments being tagged with the same molecular sequence was exceedingly improbable—a .31% chance in one instance.⁸ Ex. 10 at 2; Ehrlich Decl., ¶ 45; Ex. 2 at 2:16–19, 30:64–67, 33:1–4; Ex. 3 at 2:17–20, 30:40–43, 32:45–48; Ex. 4 at 2:16–19, 30:26–29, 32:33–36.

Also shedding light on the meaning of “non-unique tags” are methods that lie at the opposite extreme and eschew the use of tags altogether. Ehrlich Decl., ¶ 47. In these embodiments, the specifications explain that endogenous features of the parent polynucleotide molecule—basically features of the parent molecule’s own nucleotide sequence—serve as “molecular identifiers.”⁹ Ex. 2 at 9:31–47, 18:24–53; Ex. 3 at 9:13–31, 17:51–18:12; Ex. 4 at 9:14–31, 17:42–18:3.

The specifications describe the use of “non-unique tags” in their treatment of what they call the “hybrid method.” Ehrlich Decl., ¶¶ 48–54. The “hybrid method,” like methods that use “unique tags,” attaches tags to parent polynucleotide molecules. Ehrlich Decl., ¶ 49. But the tags used do not, by themselves, allow for precise (*i.e.*, unique) identification of the parent polynucleotide molecules, because other tags having identical nucleotide sequences may be attached to multiple parent polynucleotide molecules in the same sample. Ehrlich Decl., ¶¶ 48–

⁷ *B.E. Miner et al., Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR*, 32(17) *Nucleic Acids Res.* e135 (Sept. 30, 2004).

⁸ Whether a tag is “unique” can be determined with straightforward math that compares the number of distinct molecular barcode sequences and the number of relevant parent polynucleotide molecules in the sample. *See, e.g.*, Ex. 2 at 6:67–7:13; Ex. 3 at 6:67–7:13; Ex. 4 at 6:67–7:13; Ex. 10 at 2.

⁹ In these methods, the parent polynucleotide molecules are fragments of a larger molecule, each with varying length and with end points that fall at different locations in the genome.

49. The patents' hybrid-method approach identifies individual molecules by combining the information in the tags with information contained in the tagged parent polynucleotide molecule to which it is attached. Ehrlich Decl., ¶¶ 49–51; *see also* Ex. 2 at 9:31–47 (disclosing the use of a “shorter n-mer tag” together with “sheared ends” in combination to uniquely label target molecules); Ex. 3 at 9:13–29 (same); Ex. 4 at 9:15–31 (same); Ex. 2 at 18:24–53 (disclosing the use of “shear points” and “the SMI tag sequence” in combination to uniquely label target molecules); Ex. 3 at 17:51–18:12 (same); Ex. 4 at 17:42–18:3 (same).

This relationship between the claimed non-unique tags and the patents' description of the “hybrid method” is seen by the claims' further recitation that the non-unique tags must be combined with other, additional information from the tagged parent polynucleotide molecule to uniquely identify the parent polynucleotide molecules. Ehrlich Decl., ¶¶ 51–54; *see, e.g.*, Ex. 2 at claim 1 (reciting in element (e) grouping based on a non-unique tag and “same start and stop positions” to uniquely label).

Plaintiffs' proposed constructions capture the salient features of the described “non-unique tags” of the “hybrid method.” “Non-unique tags” are attached to multiple parent polynucleotide molecules and function as molecular identifiers only when combined with information from the tagged parent polynucleotide molecule.

(b) Defendant's Answering Position

(i) The “non-unique” terms and the “sufficiently/substantially unique/identifiable” terms are indefinite

The '699, '951, and '127 patents all include claims that recite “non-unique” molecular barcodes (or tags) that are attached to parent polynucleotides. However, as discussed below, the line between “unique” and “non-unique” tags in TwinStrand's patents is blurry from the outset because even Plaintiffs admit that so-called “unique” tags sometimes are in fact “non-unique.”

Moreover, as these claims were copied from Guardant’s patent applications, the term “non-unique” is not even mentioned, much less defined, *anywhere* in *any* of the patent specifications. Compounding the lack of any teaching of what “non-unique” means in the context of these claims, the patents also recite “substantially unique,” “sufficiently unique,” and “substantially identifiable” tagged DNA fragments or tags. There also is no discussion *anywhere* in *any* of the specifications of “substantially unique” tags or “sufficiently unique” tagged DNA fragments. There also is *no discussion* of the required percentage or degree of uniqueness, nor *any explanation* of how a POSITA would determine whether a tag or a tagged DNA fragment is non-unique, sufficiently unique or substantially unique.

The section 112 definiteness requirement mandates that a patent provide “clear notice of what is claimed” and a claim is indefinite if it fails to inform a POSITA of the scope of the invention with reasonable certainty. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901, 909 (2014). Further, while terms of degree such as “substantially” and “sufficiently” are not inherently indefinite, the patent must provide some standard for measuring that degree so a POSITA can determine the bounds of the claim. *In re Mobile Telecommunications Technologies*, 265 F. Supp. 3d 434, 474 (D. Del. 2017) (citing *GE Lighting Solutions, LLC v. Lights of Am., Inc.*, 663 F. App’x. 938, 940 (Fed. Cir. 2016)). The TwinStrand asserted claims clearly fail these requirements because the bounds of the “non-unique,” “sufficiently unique,” “substantially unique” and “substantially identifiable” claim limitations cannot be determined by a POSITA with any reasonable certainty and because the patents do not provide any objective standard by which to determine whether a tag or tagged fragment is non-unique, substantially unique, sufficiently unique or substantially identifiable.

- (ii) **The intrinsic evidence fails to provide any guidance as to where the line is drawn among unique,**

substantially/sufficiently unique and non-unique tag fragments and tags

The asserted claims provide no guidance as to what constitutes “non-unique,” “substantially unique,” “sufficiently unique” or “substantially identifiable.” Ex. 20, Quackenbush Decl. ¶ 72. Claims 1 and 20 of the ’699 patent, claim 21 of the ’951 patent and claim 26 of the ’127 patent recite non-uniquely tagged DNA fragments that are “substantially unique” or “substantially identifiable.” Independent claim limitation 1.b of the ’699 patent is illustrative:¹⁰

1.b) converting the population of circulating DNA molecules into a population of non-uniquely tagged parent polynucleotides, wherein **each of the non-uniquely tagged parent polynucleotides comprises** (i) a sequence from a circulating DNA molecule of the population of circulating DNA molecules, and (ii) an identifier sequence comprising one or more polynucleotide barcodes, such that **each non-uniquely tagged parent polynucleotide is substantially unique with respect to other non-uniquely tagged parent polynucleotides** in the population;

Claim 24 of the ’951 patent is slightly different in that it claims duplex tags that are “sufficiently unique” from each other so that the tagged DNA fragments can be “substantially differentiated”:

24. The method of claim 1, wherein the tagging step further comprises attaching duplex tags to ends of each of said double-stranded polynucleotide molecules in said sample, and **wherein said set of duplex tags comprise tag sequences that are sufficiently unique so that individually tagged double-stranded polynucleotide molecules can be substantially differentiated** from other tagged double-stranded polynucleotide molecules.

Nothing in any of these claims provides any guidance as to how to identify, much less distinguish among, non-unique, substantially unique, sufficiently unique or substantially

¹⁰ Claim 20 of the ’699 patent and claim 21 of the ’951 patent are similar to claim 1 of the ’699 patent. Claim 26 of the ’127 patent is slightly differently and recites: “The method of claim 22, wherein the library comprises at least a subset of non-uniquely tagged double-stranded adapter-DNA molecules, and **wherein non-uniquely tagged double-stranded adapter-DNA molecules are substantially identifiable with respect to other non-uniquely tagged double-stranded adapter-DNA molecules** in the bodily sample using the one or more barcode sequences and DNA fragment-specific information.” (Emphasis added).

identifiable tagged DNA fragments and tags. The claims thus plainly fail to provide any objective boundaries of their scope. Ex. 20, Quackenbush Decl. ¶¶ 73-74.

Given that the patents provide no such guidance, Plaintiffs instead point to the specifications' extensive discussion of the term "unique," a term that does not actually appear in the claims. *Supra* at 11-12. Plaintiffs' apparent rationale is that "substantially/sufficiently unique" and "non-unique" tags can be understood by reference to the patents' discussion of "unique" tagging and to methods that do not employ any tagging whatsoever, implying that anything that is neither a "unique" tag nor a tag at all must be a "non-unique" tag. *Id.* Plaintiffs' arguments to this effect simply confirm indefiniteness.

According to Plaintiffs, "unique" tags "are distinct from one another, with no two of the same tag nucleotide sequence being attached to multiple parent polynucleotide molecules, except in extremely rare instances." *Supra* at 11. By this assertion, however, Plaintiffs admit that "unique" tags can in supposedly "extremely rare circumstances" be identical such that they also would fall within the scope of their construction of "non-unique" tags. This contradictory result, where "non-unique" and "unique" overlap and mean the same thing, confirms indefiniteness.

While Plaintiffs attempt to explain away this inconsistency by arguing that this overlap happens only in "extremely rare circumstances," the evidence they cite undermines them further. Plaintiffs cite the Miner reference, which allegedly teaches that "unique" tagging results in the probability that 0.31% of the polynucleotides will be labeled with the identical tag—meaning that a so-called "unique" tag was in fact "non-unique" as least 0.31% of the time in this study. *Supra* at 12. Plaintiffs characterize 0.31% as "exceedingly improbable." But as a matter of pure commonsense, 0.31% is not "exceedingly improbable," but rather a significant and measurable fraction. If 0.31% of polynucleotides among a population of millions have the same tag, it is

guaranteed that there will be huge numbers of measurable fragments that are tagged identically. Nothing in the specification provides any sort of standard that would clarify to a POSITA the distinction between “unique” and “non-unique” in this (or any other) circumstance. Ex. 20, Quackenbush Decl. ¶ 76.

The prosecution histories, like the specifications, also fail to provide any clarity to the scope of these claim terms. Ex. 20, Quackenbush Decl. ¶ 77. The term “non-unique” only appeared in the prosecution histories of the ’699 and ’127 patents when it was added to pending claims—without any corresponding identification of adequate written description support. Ex. 27, ’699 patent file history, 5/24/19 Prelim. Amend.; Ex. 28, ’127 patent file history, 4/24/20 Amendment and Response. “Non-unique” was presented in the original claim set of the ’951 patent application, but no written description support was identified there either. Ex. 29, ’951 patent file history, 7/17/19 Application. The prosecution histories are similarly devoid of any explanation of the phrases “substantially unique,” “sufficiently unique,” and “substantially identifiable” or how they can be measured. Like “non-unique,” these terms were added to the claims during prosecution of the ’699 and ’127 patents without citation to any corresponding support in the specifications for the amendments. Ex. 27, ’699 patent file history, 5/24/19 Prelim. Amend.; Ex. 28, ’127 patent file history, 4/24/20 Amendment and Response. While these two claim terms were included in the original claim set filed in the ’951 patent prosecution, they also were unaccompanied by any supporting citation to the specification. Ex. 29, ’951 patent file history, 7/17/19 Application.

In short, the intrinsic evidence is devoid of any explanation of how to determine whether a claimed tag is non-unique, substantially unique, sufficiently unique or substantially identifiable.

(iii) Extrinsic evidence does not clarify the scope of the claims

As confirmed by Dr. Quackenbush, the patents and file histories provide no guidance to a POSITA to determine the boundaries of the “non-unique,” “substantially unique,” “sufficiently unique” or “substantially identifiable” claim limitations. Ex. 20, Quackenbush Decl. ¶¶ 77-79. Dr. Quackenbush further explains that there is no extrinsic evidence that sufficiently clarifies whether a tagged DNA fragment or a tag is “non-unique,” “substantially” or “sufficiently” unique, or “substantially identifiable.” *Id.* at ¶ 79.

(iv) Plaintiffs’ proposed constructions of the “non-unique” terms lack support and are incorrect

Plaintiffs’ argument that a “‘non-unique’ tag is just as it sounds, a tag that has a nucleotide sequence that is identical to other tags that are attached to multiple parent polynucleotide molecules in the same sample” (*supra* at 11) is *not* what Plaintiffs’ actual claim constructions provide. Instead, Plaintiffs’ constructions add the following requirement: “wherein the tag nucleotide sequence serves as a molecular identifier only when combined with other information from the tagged parent polynucleotide molecule.” There are at least two problems with this assertion. Ex. 20, Quackenbush Decl. ¶ 80.

First, Plaintiffs’ added requirement appears to provide that two non-unique tags that are identical to each other do not in fact qualify as the claimed non-unique tags unless and until they are later combined with other information that renders them unique. Plaintiffs fail to explain how two tags that are identical to each other cannot be the claimed non-unique tags until they are rendered non-unique.

Second, Plaintiffs suggest that including this added requirement is appropriate because non-unique tags, by themselves, do not “allow for precise (*i.e.*, unique) identification of the parent polynucleotide molecules because other tags having identical nucleotide sequences may

be attached to multiple parent polynucleotides in the same sample.” *Supra* at 12. However, this argument in favor of imposing a requirement that the claimed “non-unique” identifier be capable of being uniquely identifiable when combined with other information runs head-on into the fact that the claims at issue in each of the ’699, ’951 and ’127 patents **do not** require such unique identification. The two independent claims of the ’699 patent instead only require the parent polynucleotides be “substantially unique.” Ex. 2, ’699 patent, claims 1, 20. Claim 21 of the ’951 patent recites the same “substantially unique” phrase. Ex. 3, ’951, claim 21. Claim 24 of the ’951 patent requires the parent polynucleotides be tagged with tags that are “sufficiently unique” so that the parent polynucleotides are “substantially differentiated.” *Id.* at claim 24. Claim 26 of the ’127 patent requires that the tagged polypeptides be capable of being “substantially differentiated.” Ex. 4, ’127 patent, claim 26. Accordingly, while these undefined “substantially” and “sufficiently” claim requirements by themselves render the claims indefinite (as discussed above), they do not justify Plaintiffs’ proposed added requirement that the non-unique identifier is uniquely identifiable when combined with other information.

Plaintiffs attempt to bolster their position by citing the “hybrid method.” *Supra* at 12-13. However, Plaintiffs fail to advise the Court that the specifications’ discussion of the “hybrid method” is limited to the following single sentence: “A hybrid method using a combination of sheared ends and a shorter n-mer tag (such as 1 or 2 or 3 or 4 or more degenerate or semi-degenerate bases) in the adaptor may also serve as unique molecular identifiers.” *See, e.g.*, Ex. 2, ’699 patent at 9:38-42. This sparse description of the “hybrid method” fails to impart the requisite clarity to the “non-unique” claim terms as it does not even reference a “non-unique” identifier, much less provide any explanation as to what a non-unique identifier is and how, if at all, it is different than a unique identifier. Nor does it offer any guidance as to the extent of the

additional information that is required to satisfy the undefined “substantially” and “sufficiently” claim requirements. Ex. 20, Quackenbush Decl. ¶¶ 80-81.

Accordingly, because the intrinsic evidence fails to provide a POSITA any reasonable clarity as to the scope of the non-unique, substantially unique, sufficiently unique or substantially identifiable claim requirements, these claims are indefinite.

(c) Plaintiffs’ Reply Position

Guardant (at 13–20) lumps together its indefinite arguments of “non-unique” tags and barcodes with “substantially” unique. But in the claims, these terms modify distinct components in the claimed methods. In particular, “non-unique” modifies tags and barcodes whereas “substantially unique” modifies “molecular identifier.” *See, e.g.*, Ex. 2, ’699 patent, 37:49–59. This distinction is important to understand the described and claimed methods.

The patents describe and claim molecular identifiers that distinguish among, and therefore can be used to track or identify, the parent polynucleotides. Broadly speaking, the patents describe three main types of molecular identifiers. One type consists of the tags or barcodes themselves, which must have enough variety so that the tags or barcodes *alone* can be used to track and identify the parent polynucleotide. Ex. 9, Ehrlich Dec. ¶¶ 44, 46. A second type is the fragment ends or features (without using any tags) of the parent polynucleotides to track and identify the parent polynucleotides. *Id.*, ¶ 47. A third type, used in the “hybrid method,” comprises both tags and fragment information to identify the parent polynucleotides. *See, e.g.*, Ex. 3, ’951 patent, claims 1 and 25; Ex. 9, Ehrlich Dec. ¶¶ 49–53; Ex. 42, Ehrlich Reply Dec. ¶ 18. The hybrid approach allows for the use of relatively short tags. Ex. 42, Ehrlich Reply Dec. ¶ 18. Using these relatively short tags alone may not allow for enough diversity of tag sequences to track and identify parent polynucleotides. In those instances, the hybrid approach uses sequence information from the tags and from the fragments themselves, which together allow for

tracking and identification of parent polynucleotides. *See* Ex. 9, Ehrlich Dec. ¶¶ 50–53.

There is no dispute that the claims reciting “non-unique” are directed to the hybrid method, which is described in the ’699 patent (9:35–42), and the ’951 patent (9:17–24). *See also* Def. Br. at 63 (“fragment ends are used in conjunction with SMI tags to uniquely label the target sequence”), 24; Ex. 20, Quackenbush Dec. ¶¶ 80, 81.

(i) “Non-unique” tags are readily understood by skilled artisans in the context of the full scope of the invention.

In the described and claimed hybrid method, tags and barcodes are non-unique because there are not enough different tag sequences in the set to distinctly label parent polynucleotides in a population. For example, if a short 3-mer (*i.e.*, a tag having a 3-nucleotide length) is used, there are only 4^3 possible distinct tags that can be generated. Ex. 42, Ehrlich Reply Dec. ¶ 22. If the population of parent polynucleotides is larger than 4^3 , then distinct parent polynucleotides will have the same tag attached to them. *Id.* This means that the tags alone cannot reliably be used to distinguish among parent polynucleotides. The hybrid method provides informational diversity by combining the sequence information of the tags and sequence information that is endogenous to the parent polynucleotide to generate molecular identifiers. *Id.*, ¶ 18.

Plaintiffs’ construction captures this idea. And Dr. Ehrlich explains that skilled artisans can readily understand whether a set of tags or barcodes are “non-unique” by assessing whether the tags or barcodes alone can be used to distinguish among parent polynucleotides. *Id.* Indeed, a skilled artisan can readily determine the probability that the same tag or barcode will be attached to different parent polynucleotides. *Cf.* Def. Br. at 16–17; Ex. 42, Ehrlich Reply Dec. ¶ 22.

(ii) “substantially unique”

Guardant contends (at 15–16, 18–20) that “substantially unique” cannot be understood by its plain and ordinary meaning because it is directed to an unknown level of degree.

“Substantially unique” captures the concept discussed above that molecular identifiers must contain enough informational content to distinguish target DNA molecules from one another. *See, e.g.*, Ex. 2, ’699 patent, claim 1; Ex. 42, Ehrlich Reply Dec. ¶ 36; *see also Exmark Manuf. Co. Inc. v. Briggs & Stratton Power Prods. Grp., LLC*, 879 F.3d 1332, 1346 (Fed. Cir. 2018) (“All that is required is some standard for measuring the term of degree.”). Quackenbush agrees: “the term ‘substantially unique’ [] presumably encompasses tagged DNA molecules that are sufficiently distinguishable from other tagged DNA molecules in the population based on sequence.” Ex. 43, Quackenbush IPR Dec. ¶ 86. A skilled artisan, based on the ’699 patent disclosure and knowledge of how to create molecular identifiers, can figure out how much information is needed for a molecular identifier to be able to distinguish parent polynucleotides from one another. Ex. 42, Ehrlich Reply Dec. ¶ 38. Accordingly, “substantially unique” is not indefinite. *See, e.g., Enzo Biochem Inc. v. Applera Corp.*, 599 F.3d 1325, 1328, 1333–36 (Fed. Cir. 2010) (holding the term “not interfering substantially” in patents concerning “various techniques for labeling and detecting nucleic acids, such as DNA and RNA,” is not indefinite); *Exmark*, 879 F.3d at 1346 (affirming that “elongated and substantially straight” is not indefinite in light of the specification) (collecting cases); *Apple Inc. v. Samsung Elecs. Co., Ltd.*, 786 F.3d 983, 1003 (Fed. Cir. 2015), *rev’d on other grounds and remanded*, 137 S. Ct. 429 (2016) (affirming that skilled artisans would understand “substantially centered” based on the patent disclosure); *Seattle Box Co., Inc. v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 826 (Fed. Cir. 1984) (affirming district court finding that “substantially equal to” is not indefinite); Ex. 45, *Ansell Healthcare Prods. LLC v. Reckitt Benckiser LLC*, C.A. No. 1:15-cv-00915-RGA, D.I. 134, slip. op. at 7 (D. Del. Mar. 16, 2017) (finding “substantially” and “substantially conchoidal fracture” are not indefinite and “substantially” to mean “to a large extent, but not necessarily

completely”).

At the same time, the parties agree that there is always some probability that different parent polynucleotides will have the same molecular identifiers—no matter how many distinct molecular identifiers are used. Ex. 44, Quackenbush Tr. at 191:7–15, 17–21 (stating the chance that multiple fragments could be tagged with the same SMI could be directed asymptotically to zero). That is why “unique” is modified by “sufficiently,” “substantially,” and the like in the claims. Courts have routinely found similar claims non-indefinite. *See, e.g., Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002) (finding “substantially constant wall thickness” not to be indefinite because the term “describe[s] the invention with precision appropriate to the technology”); *Ruckus Wireless, Inc. v. Netgear, Inc.*, 2013 WL 6627737, at *4 (N.D. Cal. Dec. 16, 2016) (declining to find “substantially omnidirectional” as indefinite and construing it pursuant to real-world concerns “warranted by the nature of the invention”); *see also Ecolab, Inc. v. Envirochem, Inc.*, 264 F.3d 1358, 1367 (Fed. Cir. 2003) (“like the term ‘about,’ the term ‘substantially’ is a descriptive term ‘commonly used in patent claims ‘to avoid a strict numerical boundary to the specified parameter.’”).

To be sure, Guardant’s patents define “unique” so as to allow for as much as 5% of molecules to share the same tag. Ex. 5, ’063 patent, 18:61–66. By comparison, Miner’s 0.31% tag sharing falls well under Guardant’s own threshold. So Guardant’s claim that Miner discloses a “significant and measureable fraction” (at 16) misses the mark. The point of substantially or sufficiently unique identifiers in the claims is to allow one to distinguish between parent polynucleotides. That this can be accomplished with a minuscule percentage of molecules sharing identifiers does not make the terms indefinite.

(d) Defendant’s Sur-Reply Position

Plaintiffs fail to identify a reliable way for ordinary artisans to apply the key

“unique/non-unique” claim terms based on the intrinsic record or otherwise. The deposition of Dr. Ehrlich starkly confirms the indefiniteness of these terms.

Plaintiffs state that the claims-in-suit cover two different categories of the invention: unique versus *non*-unique tagging approaches. Ex. 9, Ehrlich Decl. ¶¶46, 49. Dr. Ehrlich testified that Claim 1 of the ’127 patent, for example, covers the unique tagging approach, while other claims cover the non-unique tagging approaches that Plaintiffs call the “hybrid” approach. Ex. 48, Ehrlich Tr. 119:14-120:12. Thus differentiating between unique versus non-unique tagging is vital for skilled artisans to understand the scope of the different claims at issue.

Plaintiffs fail to address the critical indefiniteness problem of how to reliably distinguish between unique versus *non*-unique tagging. Dr. Ehrlich confirmed that unique tagging and non-unique tagging are mutually exclusive, but that does not answer the question of demarcation between the two terms. *Id.* 61:6-7 (“A non-unique tag is different from a unique tag.”); 55:11-14.

Dr. Ehrlich confirmed Plaintiffs’ position that “unique” tagging in fact includes instances of non-unique tags. *Id.* 59:15-18. Instances of non-unique tags (the same tag applied to different DNA fragments) in a library of DNA is called “tag-sharing.” The widespread existence of tag-sharing in unique tagging immediately raises the question of how much “tag-sharing” is tolerable before unique tagging actually becomes non-unique tagging. Dr. Ehrlich’s attempt to answer this key claim-boundary question is contradictory and unavailing.

In his declaration, Dr. Ehrlich posited that tag-sharing was acceptable in unique tagging so long as it is “exceedingly improbable” while Plaintiffs’ brief used the phrase “extremely rare.” Ex. 9, Ehrlich Decl. ¶ 45; *Supra* at 11. Dr. Ehrlich could not identify meaningfully what these phrases mean or how they would be applied by ordinary artisans. Instead, he testified that “the

boundary line between unique tags and non-unique tags” is somewhere between 0.31% and 5% tag sharing. Ex. 48, Ehrlich Tr. 63:12-64:2. But he also testified 5% tag-sharing is not “exceedingly improbable.” *Id.* 63:2-5. Then he testified that his own “boundary” between unique versus non-unique tagging is 1% tag-sharing as a general rule that is not “experiment-specific.” *Id.* 64:19-65:10. He was unable to identify how a skilled artisan would select a tag-sharing boundary between 0.31% and 5% tag sharing. *Id.* 64:10-18.

To try to mop up this mess, Plaintiffs had to cross-examine their own expert to ask how “a person of ordinary skill in the art could determine whether the parent polynucleotide molecules of the claims were uniquely tagged or non-uniquely tagged in the context of inventions.” *Id.* 137:12-138:3. He responded with yet another inconsistent and unexplained measure: “You would look at the sequence and you could determine from the sequence the *length* of the tag.” *Id.*¹¹

In sum, the non-unique term is indefinite because Plaintiffs have failed to identify a reliable way for ordinary artisans to differentiate between unique and non-unique tagging. In terms of the permissible tag-sharing at the boundary of unique versus non-unique, Plaintiffs and their expert have variously identified broad numerical ranges with no way to pick within the range, vague verbal descriptions such as “exceedingly improbable” that conflict with the numerical range, and the totally different metric of tag length. That fails to offer a reliable scope to these claim terms.

Plaintiffs insist on treating the “substantially unique” identifier as a separate term, but this distinct treatment does not save the term from indefiniteness. Dr. Ehrlich essentially admitted that the patent does not explain how to determine whether an identifier is “substantially unique”:

¹¹ Emphasis supplied throughout.

Q. But to answer my question, the patent, with or without Miner, doesn't tell you what tolerance is acceptable for an identifier to be substantially unique, correct?

A. It's not what the, it's not what the patent is about.

Id. 93:22-94:5. Dr. Ehrlich punted on this critical issue, stating that “it’s really going to be up to the investigator, you know, as to what their tolerance is.” *Id.* 90:21-91:16.

Plaintiffs have failed to identify any reliable measure as to whether an identifier is “substantially unique” and this term is indefinite too. Dr. Ehrlich’s declaration states that a POSA would just rely on “common sense” to know the bounds of “substantially unique.” Ex. 42, Ehrlich Reply Decl. ¶ 38. This fails to provide “clear notice of what is claimed” and this term is also indefinite. *Nautilus*, 572 U.S. at 909.

2. The “high accuracy” terms

Claim Term	Patent, Claim	Plaintiffs’ Proposed Construction	Defendant’s Proposed Construction
“high accuracy sequence reads”	’631 patent, claims 1, 16	Plain and ordinary meaning; not indefinite	Indefinite
“high accuracy consensus sequence read”	’631 patent, claims 1, 4, 7, 16, 23	Plain and ordinary meaning; not indefinite	Indefinite

(a) Defendant’s Answering Position

The ’631 patent claims describe a method of “generating high accuracy sequence reads” that involves generating a “high accuracy consensus sequence read.” *See, e.g.*, Ex. 1, ’631 patent, claim 1. However, neither the intrinsic nor extrinsic evidence provides any guidance as to the scope of either of these “high accuracy” phrases. These claims are therefore indefinite.

(i) Intrinsic evidence does not clarify claim scope

The claims do not themselves provide any explanation or context for what “high accuracy” encompasses. Ex. 20, Quackenbush Decl. ¶¶ 83-84. Nor are the bounds of a “high accuracy sequence read” or “high accuracy consensus sequence read” explained in the

specification. Indeed, neither of these phrases is ever used in the specification. *Id.* ¶ 84.

The file history is similarly lacking. The only guidance to be gleaned from the file history is that during prosecution applicants disclaimed any equivalency between a “high accuracy” sequence read or consensus sequence read and an “error corrected” sequence read or consensus sequence read. The originally filed claims of U.S. Patent App. No. 15/660,785 included a claim to “a method of generating an error corrected double-stranded consensus sequence.” Ex. 30, ’631 patent File History, 7/26/17 Application. That original claim was cancelled, and additional claims were added in a preliminary amendment that similarly recited “a method of generating an error corrected sequence read.” Ex. 31, 2/9/18 Prelim. Amend. The examiner then rejected all the pending claims as anticipated by Steemers et al. WO2012/061832 because, in part, Steemers teaches “a method of generating an error corrected sequence read of a double-stranded target nucleic acid molecule.” Ex. 32, 4/10/2018 Non-final Rejection. Applicants then amended their pending claims by, among other changes, replacing the phrase “an error corrected sequence read” with the phrase “high accuracy sequence reads,” and by replacing the phrase “generating an error corrected sequence read” with the phrase “generating a high accuracy consensus sequence read.” Ex. 33, 7/10/18 Amend. Applicants argued that Steemers did not teach, among other elements, generating high accuracy sequence reads or a high accuracy consensus sequence read. *Id.* The claims then issued because, according to the examiner, Steemers did not teach generating high accuracy sequence reads. Ex.34, 12/27/18 Notice of Allowance.

While the file history makes plain that “high accuracy” sequence reads and consensus sequence reads are not the same as “error corrected” sequence reads and consensus sequence reads, it fails to offer any guidance as to what accuracy rates constitute “high accuracy.” Does an accuracy rate of 80% constitute the threshold of high accuracy? 90%? 99%? 99.9%?

99.999%? The intrinsic record provides no instruction to a POSITA as to how high the accuracy must be to satisfy the claim. Ex. 20, Quackenbush Decl. ¶¶ 85-87.

(ii) Extrinsic evidence does not clarify claim scope

As Dr. Quackenbush explains, there is no industry standard as to what “highly accurate” means and these two claim phrases have no accepted plain meaning to a POSITA. Ex. 20, Quackenbush Decl. ¶¶ 88-89. In this regard, the accuracy of a sequence read is dependent on multiple factors and reflects, in part, the error rate of the underlying DNA sequencing technology used and the location of the fragment. Moreover, certain regions of the genome may have characteristics that make sequencing more error prone, such as regions with highly repetitive sequences. The accuracy of a consensus sequence read also is dependent on factors including fragment length, read depth (the number of reads of a particular fragment), and the computational methods used to compile the data. *Id.* at ¶88. The number and variety of the factors that impact the accuracy of a sequence read in any given case underscore the lack of any accepted meaning of the phrases “highly accurate sequence read” and “highly accurate consensus sequence read.” *Id.* The claims are therefore indefinite because they “fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.” *Nautilus*, 572 U.S. at 901.

(b) Plaintiffs’ Reply Position

The “high accuracy” claim terms are not indefinite. Examining the term in the *context of the entire claim* (as one must) is informative because the claims themselves specify what a “high accuracy consensus sequence read” is and how it is generated.

The “high accuracy” terms are used in connection with “sequence reads,” which are the data produced by the “sequencing” step of the claims (*e.g.*, producing a nucleotide sequence such as “ACTGT...”). And the claims themselves specify precisely that “high accuracy consensus

sequence” reads qualify as such because they include only the nucleotide positions where the top- and bottom-strand data match via complementary base pairs:

generating a high accuracy consensus sequence read for each of the double-stranded target nucleic acid molecules in the population **that includes only the nucleotide positions where the compared first and second strand sequence reads are complementary.**

Ex. 1, ’631 patent, claim 1 (38:37–41) (emphasis added), claim 16 (40:27–31) (emphasis added).

The claims not only spell out what a “high accuracy consensus sequence read” means, but also recite the steps needed to generate them.¹² There is a “sequencing” step that produces “sequence reads.” *E.g., id.* at 37:54–57. The claims then delineate the steps in which this data (claimed as “reads”) are analyzed or manipulated. The “reads” are (i) “group[ed]” in families based on distinguishing features, (ii) “separat[ed]” into sets of first and second strands¹³, (iii) “confirm[ed]” that at least one first and second strand are present, and (iv) “compar[ed].” *E.g., id.* at 37:58–38:30. Lastly, the “generating” step recites that these “reads” are made to be “high accuracy consensus reads” in that they include only positions where the nucleotides are complementary. *E.g., id.* at 38:37–41.

Guardant’s indefiniteness argument (at 27–28) entirely misses the point of the claims. It frames the term “high accuracy” as though it were used to demarcate reads that are more accurate than others. But, as shown above, that is not what is claimed. The generating step is just another step that analyzes or manipulates the “reads.” There is no requirement that the “reads” achieve any particular level of accuracy or lack any errors. Indeed, the dependent claims (*e.g.*, claim 23) recite that where the first and second reads do not match—due to errors during

¹² The preambles recite the purpose of the methods, namely “generating high accuracy sequence reads.”

¹³ In the claims, first and second strand reads reflect the top and bottom complementary strands.

sequencing—those positions should be scored as artifacts, not as mutations. Ex. 1, '631 patent, 40:55–60. And nothing in the prosecution history cited by Guardant (at 27) indicates that the Examiner required any particular level of accuracy to be understood.

In short, the claims themselves make clear that “high accuracy [consensus] sequence reads” are reads where nucleotide base calls on the top strand matches its complement in the bottom strand. Ex. 42, Ehrlich Reply Dec. ¶ 70. What is more, a skilled artisan would understand that, among other things, is the method harnesses the redundancy, or complementarity, between parent DNA strands to ensure accuracy of the resultant sequence read of the claimed method. *Id.*, ¶ 68; *see also* Ex. 1, '631 patent, 16:45–17:5; *id.* at 17:7–12. After the steps of the claims have been followed, if a mutation exists in the consensus sequence read (from both the top and bottom DNA strands) representing a specific target, it is a true mutation. Ex. 1, '631 patent, 21:52–59. If the mutation (difference between sequence reads and a reference sequence) exists in an identified nucleotide position where the top and bottom strands are non-complementary, it is not a true mutation, but rather “noise.” *See id.* at 16:45–59; Ex. 42, Ehrlich Reply Dec. ¶ 68. And the dependent claims state that non-complementary reads containing noise should be disregarded. Ex. 1, '631 patent, 40:55–60. Accordingly, “high accuracy” is reasonably clear and understood by its plain and ordinary meaning in the context of the claim language.

(c) Defendants’ Sur-Reply Position

To try to side-step the indefiniteness of the “high accuracy” terms, Plaintiffs argue that the term is superfluous and can be eliminated from the claims altogether, stating that “high accuracy sequence reads” and “high accuracy consensus sequence reads” do not require the reads “to achieve any particular level of accuracy or lack any errors.” *Supra* at 29-30. Dr. Ehrlich testified that “high accuracy” could be eliminated from the claim without a change in scope. Ex. 48, Ehrlich Tr. 41:3-8. This attempt to empty this term of meaning is legally unsupported.

“Claims must be ‘interpreted with an eye toward giving effect to all terms in the claim’” and avoiding “a claim construction which would render a claim limitation meaningless.” *Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1257 (Fed. Cir. 2010) (citations omitted); *see also Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 951 (Fed. Cir. 2006) (holding a claim construction that reads limitations out of a claim is “contrary to the principle that claim language should not [be] treated as meaningless”).

Dr. Ehrlich’s testimony reinforces the indefiniteness of Plaintiffs’ claims. In view of the claim term “high accuracy,” he testified “that there are multiple ways of looking at and predicting error.” Ex. 48, Ehrlich Tr. 48:21-49:9. Further, “the most common methodology or metric is going to be error rate for, you know, which is what is used in claims 10 and 11.” *Id.* 48:7-19. In this testimony, Dr. Ehrlich is referencing the presence of dependent claims that include a required error rate in the ’699 patent.

But Dr. Ehrlich never identifies a particular error rate for “high accuracy” or how otherwise to measure the required “high accuracy” of the claims. He tried to eschew a quantitative analysis altogether by testifying that any improvement from the invention is sufficient to meet the “high accuracy” claim requirement: “With regard to putting a number on it, as I said, you know, it’s going to be anything, you know, which is substantially better, you know, than the baseline error rate.” *Id.* 52:3-13. Dr. Ehrlich ended up admitting he has no opinion whether there is a quantitative benchmark that can be used to evaluate whether the claimed “high accuracy” is satisfied:

- Q. Is there any quantitative benchmark that a person of ordinary skill in the art can use to determine high accuracy as that term is used in the claims of the 631 patent, whether or not you think it’s necessary?
- A. Yeah, I, I don’t have a, I don’t have an opinion on that.

Id. 53:2-6. Plaintiffs’ attempt to duck the indefiniteness of the claim term “high

accuracy” by denying that the term has any meaning at all should be rejected and the term found “indefinite.” Plaintiffs have failed to identify a reliable way to measure the required “high accuracy.” Plaintiffs do not dispute that the intrinsic record offers no guidance other than the fact that Plaintiffs disclaimed “error corrected” [consensus] sequence reads during prosecution. *See supra* at 27. Dr. Ehrlich’s proposed definition cannot be correct in light of the prosecution history and there is no other description of the level of accuracy required.

3. “fragment features” and “DNA fragment-specific information”

Claim Term	Patent, Claim	Plaintiffs’ Proposed Construction	Defendant’s Proposed Construction
“fragment features”	’631 patent, claim 16, 18	Plain and ordinary meaning; not indefinite	Indefinite
“DNA fragment-specific information”	’127 patent, claim 22	Plain and ordinary meaning; not indefinite	Indefinite

(a) Defendant’s Answering Position

The claim terms “fragment feature” and “fragment-specific information” are indefinite because it is unknown what “features” or “information” are encompassed by the claims. Neither of these terms appears anywhere in the patents’ specifications or file histories, and a POSITA is therefore left to guess what these claim phrases encompass. For example, do the claimed “features” and “information” encompass any or all of the size, specific nucleotide pattern, overall nucleotide composition, nucleotide modification, or any other property of a DNA fragment? The patents shed no light on the answer to this question. Ex. 20, Quackenbush Decl. ¶¶ 90-91. Accordingly, because these claim terms do not give notice to a POSITA of the scope of the claims, they are invalid as indefinite. *Nautilus*, 572 U.S. at 901.

(i) Intrinsic evidence does not define the claim scope

1) “fragment features”

Claims 16 and 18 of the ’631 patent do not provide any guidance as to what is

encompassed by the claimed “fragment features.” Claim 16 includes the limitations “wherein each double-stranded target nucleic acid molecule comprises **one or more fragment features** that distinguish the individual double-stranded target nucleic acid molecules from other double-stranded target nucleic acid molecules. . . . grouping the first and second strand sequence reads into a family of sequence reads by identifying the **one or more distinguishing fragment features** shared by each strand . . . ” Ex. 1, ’631 patent, claim 16 (emphasis added). The claim language sheds no light on what “one of more fragment features” fall within the scope of the claim. Claim 18 only compounds the lack of clarity by claiming that the “**one or more fragment features** includes a shear point or other fragment region, or a combination thereof.” *Id.* at claim 18 (emphasis added). “Fragment region” is undefined in the specification and describing a “fragment feature” as a “fragment region” without delimiting the size or location of the region does nothing to meaningfully define the scope of the claimed “fragment features.”

“Fragment features” does not appear anywhere in the specification. Moreover, the term “fragment features” was added to pending claims 53 and 55 of U.S. Patent Appl. No. 15/660,785 in a preliminary amendment without any corresponding citation to the specification for support. Ex. 31, ’631 patent file history, 2/9/2018 Preliminary Amendment.

The subsequent prosecution history likewise fails to provide any clarity as to the meaning of the term. The examiner recited the term “fragment features” in her non-final rejection dated 4/10/2018, stating that the prior art Steemers reference teaches “pairing the first and second strand sequence reads based on one or more fragment features shared by each strand of the double-stranded target nucleic acid molecule and confirming the presence of at least one first strand sequence read and at least one second strand sequence read.” Ex. 32 at 4/10/2018 Non-Final Rejection. Steemers uses the term “feature” to describe target nucleic acids in an array

format, where they are “typically coupled to a surface in a spatially distinguishable manner. . . .

The array can include a single copy of a target nucleic acid at each site (also referred to as a feature) or multiple copies having the same sequence can be present at each site or feature.” Ex. 35, Steemers at p. 54, lines 2-17. However, the prosecution history does not purport to define the term “fragment features” as being coextensive with the use of fragment features in Steemers, and therefore fails to provide the requisite clarity as to the scope of that claim term.

2) “DNA fragment specific information”

Claims 22 and 26 of the ’127 patent claims do not provide guidance as to what information falls within the scope of this claim term. Independent claim 22 recites “grouping the strand sequence reads into families based on i) the barcode sequence, and ii) **DNA fragment-specific information.**” Ex. 4, ’127 patent, claim 22 (emphasis added). Dependent claim 26 is similar, reciting the use of “one or more barcode sequences and **DNA fragment-specific information.**” *Id.* at claim 26 (emphasis added). At most, claims 22 and 26 teach that both DNA fragment-specific information and barcode sequences can be used to group DNA fragments into families—thus implying that DNA fragment-specific information is distinguishable from barcode-specific information. This distinction, however, fails to tell a POSITA what the claimed information is.

The phrase “DNA fragment-specific information” is neither mentioned nor defined in the specification. During prosecution of U.S. Patent Appl. No. 16/503,382, the phrase “fragment-specific feature” was introduced in new claim 60. Ex. 36, ’127 patent file history, 8/8/2019 Prelim. Amend. (emphasis added). The examiner rejected the pending claims as obvious over Otwinowski et al. WO2013/181170, noting that the reference teaches “wherein the at least one sequence read derived from the original first strand and the at least one sequence read derived from the original second strand can be related based on an adapter tag sequence, a fragment-

specific feature, or a combination thereof.” Ex. 37 at 1/24/2020 Non-final Rejection.

Otwinowski teaches grouping fragments by fragment sequence, length, and randomized barcode sequence. Ex. 38, WO2013/181170 at [12]. In response, applicants added new claims 64 and 68 that included the phrase “DNA fragment-specific information.” Ex. 28, ’127 patent file history, 4/24/2020 Response to Non-Final Office Action (emphasis added). The claims were allowed shortly thereafter. There is no further explanation in the prosecution history as to what is encompassed by the term “DNA fragment-specific information” of claims 22 and 26, or how it is distinct from the “fragment-specific feature” of claim 18.

(ii) Extrinsic evidence does not provide the requisite clarity

“Fragment features” as used in the ’631 patent and “DNA fragment-specific information” as used in the ’127 patents could, for example, encompass any fragment length from one nucleotide to the entire length of the fragment. Ex. 20, Quackenbush Decl. ¶ 97. Alternatively, they also could refer to the nucleotide sequence of either a portion of the fragment or the whole fragment. *Id.* There is simply no way to discern from the intrinsic evidence what precisely is encompassed by these phrases. As such, they are indefinite.

(b) Plaintiffs’ Reply Position

The meaning of “fragment” is not in dispute. *See, e.g.*, Ex. 44, Quackenbush Tr. at 12:17–21. The parties only dispute the meaning of “features” and “information.” A skilled artisan would readily understand from the context of the ’631 and ’127 patents the features and information that fall within the scope of the claimed invention.

Each side agrees that a “fragment” is a piece of a larger nucleic acid molecule. *Id.* at 12:17–21 (stating fragment features are a “piece of a nucleic acid molecule”). As such, all of the claimed fragments have sugar-phosphate backbones with nitrogenous bases (A, C, G, and T) along their length. Ex. 42, Ehrlich Reply Dec. ¶ 47. As a result, fragment-specific—in any

context—has very few features or information beyond a fragment’s size and nucleotide sequence, *e.g.*, “ACTGT...” *Id.*, ¶ 53 And, in the context of the claims, the range of possible features or information that a fragment might possess is narrowly restricted to sequence information. *See, e.g.*, Ex. 1, ’631 patent, 40:9–17 (stating “sequence reads” are grouped by “fragment feature,” which must occur after sequencing); Ex. 4, ’127 patent, 40:8–11 (“sequencing a plurality of strand copies to obtain strand sequence reads comprising...DNA fragment-specific information”); Ex. 42, Ehrlich Reply Dec. ¶ 54.

For example, in claim 22 of the ’127 patent, “fragment-specific information” is used as a basis to group sequence reads.¹⁴ Ex. 4, ’127 patent, 40:12–16. And the sequencing step of the claim (which provides antecedent basis for “fragment-specific information”) makes clear that “fragment-specific information” is just sequence data. *Id.* at 40:8–11. That is because the sequencing step recites that “sequence reads” comprise “fragment-specific information.”¹⁵ *Id.*

Likewise, in claim 16 of the ’631 patent “fragment features” are present after the sequencing step and are used to group sequence reads, so these features are also sequence reads. Ex. 1, ’631 patent, 40:13–17. *See id.* (reciting “grouping the first and second strand sequence reads”); Ex. 42, Ehrlich Reply Dec. ¶¶ 49–52.

Skilled artisans would know that these terms are circumscribed by the type of information obtainable from sequence reads so long as the data, information, or features

¹⁴ “Reads” are just the nucleotide-sequence data generated by sequencing. Ex. 42, Ehrlich Reply Dec. ¶ 53.

¹⁵ Guardant appears to argue (at 34) that there is some confusion about the meaning of “bar code information” and “DNA fragment-specific information.” But as Dr. Quackenbush explains (and as is clear from the claims), both of these “information” are sequencing information of the “adaptor-DNA molecule.” *See* Ex. 43, Quackenbush IPR Dec. ¶ 58. The adaptor-DNA molecule is formed by attaching an adaptor, which includes a barcode, to a DNA fragment in the first step of the method. Ex. 4, ’127 patent, 39:56–40:4.

“distinguish one molecule from another.” *See* Ex. 44, Quackenbush Tr. at 87:25–88:11; *see also* Ex. 1, ’631 patent, 39:41–48 (“fragment features that distinguish the individual double-stranded target nucleic acid molecules from other double-stranded target nucleic acid molecules”); Ex. 4, ’127 patent, 40:12–16 (similar); Ex. 42, Ehrlich Reply Dec. ¶¶ 54, 55.

(c) Defendants’ Sur-Reply Position

Plaintiffs argue that “fragment feature” and “DNA fragment-specific information” “has very few features or information beyond fragment size and nucleotide sequence . . . and in the context of the claims, [the features or information] is restricted to sequence information.” *Supra* at 35-36. Yet, Dr. Ehrlich admitted that, for example, fragment weight is in fact “fragment features.” Ex. 48, Ehrlich Tr. 68:1. If the claims were intended to only cover DNA sequence, they easily could have used that term rather than the expansive and ill-defined terms that were used.

4. “degenerate ... sequence(s)” and “semi-degenerate ... sequence(s)”

Claim Term	Patent, Claim	Plaintiffs’ Proposed Construction	Defendant’s Proposed Construction
“degenerate ... sequence(s)”	’631 patent, claims 1, 12, 13, 15; ’951 patent, claim 23; ’127 patent, claim 13	a nucleotide sequence that is known or unknown in which every nucleotide position is unrestricted in its nucleotide variability	[single molecule identifier (SMI) / oligonucleotide] sequence in which all of the nucleotides have been randomly generated
“semi-degenerate ... sequence(s)”	’631 patent, claims 1, 12, 13, 15; ’951 patent, claim 23; ’127 patent, claim 13	a nucleotide sequence that is known or unknown in which at least one nucleotide position is fixed or restricted in its nucleotide variability	[single molecule identifier (SMI) / oligonucleotide] sequence in which some of the nucleotides have been randomly generated

(a) Plaintiffs' Opening Position

Certain of Plaintiffs' patent claims recite that the barcodes and single-molecule identifiers (SMIs) (*i.e.*, tags) are comprised of "degenerate" and "semi-degenerate" sequences. Ex. 1 at claims 1, 12, 13, 15; Ex. 3 at claim 23; Ex. 4 at claim 13. "Degenerate" and "semi-degenerate" sequences are terms of art that describe the variability with which nucleotide bases (*i.e.*, A, C, G, and T) may occupy the positions of a molecular sequence. Ehrlich Decl., ¶¶ 58–60. The parties' competing constructions differ in the character and extent of that variability. In particular, the parties generally agree that the claim term "degenerate ... sequence(s)" requires some type of variability at *all* nucleotide positions, and the term "semi-degenerate ... sequence(s)" requires some type of variability at *one or more* nucleotide positions. The parties' dispute centers on one discrete issue: whether degeneracy connotes *variability* at each nucleotide location (as proposed by Plaintiffs), or *randomness* at generation (as proposed by Guardant). Plaintiffs' position is correct.

(i) Plaintiffs' proposed constructions are supported by the intrinsic record and extrinsic evidence.

Plaintiffs' patent specifications describe a degenerate sequence as a sequence wherein any nucleotide (A, C, G, or T) may be present at each nucleotide position. The 12-mer "degenerate nucleotide sequence" described in the specifications' Example 1 shows why degeneracy carries this meaning. There, the specifications report that the "degenerate" 12-mer barcode (or "tag") sequence used in this example was embedded within a larger nucleotide sequence called an adaptor. Ex. 1 at 19:14–42, 20:38–58; Ex. 3 at 19:18–47, 20:43–63; Ex. 4 at 19:9–36, 20:34–55. The specifications identify the molecular sequence of two strands ("primer" and "template") that were combined to form the adaptor and designates the 12 base positions embedded within the template strand that comprise the degenerate barcode with the letter "N."

Ex. 1 at 19:40, 33:67; Ex. 3 at 19:45, 35:12; Ex. 4 at 19:35, 35:6. The other base positions (not part of the barcode) that comprise Example 1's adaptor are restricted or fixed as either an (A, C, G, or T), as shown below.

the primer strand:

(SEQ ID NO: 1)

AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCTCT

TCCGATCT;

and

the template strand:

(SEQ ID NO: 2)

/5phos/ACTGNNNNNNNNNNNNAGATCGGAAGAGCACACGTCTGAACTC

CAGTCAC.

Ex. 1 at 19:32–42 (annotated); Ex. 3 at 19:37–47 (annotated); Ex. 4 at 19:27–37 (annotated).

According to the specifications, “n is a, c, g, or t.” Ex. 1 at 33: 63; Ex. 3 at 35:8; Ex. 4 at 35:2. That is, the specifications contemplate that each nucleotide in the sequence can be any of the four possible nucleotides—*i.e.*, every nucleotide position is unrestricted in its nucleotide variability. Ehrlich Decl., ¶ 61.

The specifications also support Plaintiffs' proposed construction that “semi-degenerate ... sequence[s]” means “at least one nucleotide position is fixed or restricted in its nucleotide variability.” Ehrlich Decl., ¶ 62. In particular, the specifications explicitly state nucleotide sequences “need not contain all possible bases at each position.” Ex. 1 at 7:22–23; Ex. 3 at 7:30–31; Ex. 4 at 7:30–31. This disclosure describes an alternative version of the tag described in Example 1, wherein, for example, the first “N” in the 12-mer barcode sequence is fixed or restricted and must be thymine (T). Ehrlich Decl., ¶ 62. So modified, this alternative version of the tag described in Exhibit 1 would be considered semi-degenerate. *Id.*

The specifications further support Plaintiffs' proposed constructions that these degenerate

and semi-degenerate sequences may be known or unknown. For example, the specifications state that these sequences “may be generated by preparing and annealing a library of individual oligonucleotides of *known* sequence.” Ex. 1 at 7:23–27 (emphasis added); Ex. 3 at 7:31–35 (emphasis added); Ex. 4 at 7:31–35 (emphasis added). The specifications further state that a double stranded degenerate or semi-degenerate SMI sequence “may be *designed* with appropriate regions of self-complementarity” and “a set of nucleotides of known sequences ... can be synthesized on an array, or by any other suitable method known in the art.” Ex. 1 at 13:15–39 (emphasis added); Ex. 3 at 13:22–50 (emphasis added); Ex. 4 at 13:14–42 (emphasis added). As Dr. Ehrlich explains, a skilled artisan would have understood that these sequences can be a known, designed sequence. Ehrlich Decl., ¶¶63–65. Thus, the specifications indicate that the claimed degenerate or semi-degenerate sequences can be known or unknown. *Id.* Moreover, Guardant’s proposed constructions do not necessarily exclude this aspect of Plaintiffs’ proposed constructions.

The extrinsic evidence supports Plaintiffs’ proposed constructions. As Dr. Ehrlich explains, as of the priority date, the terms “semi-degenerate” and “partially degenerate” were well known and often used by skilled artisans interchangeably and in a manner consistent with Plaintiffs’ proposed constructions. *Id.* at ¶¶66–67 (citing Ex. 11 (*D. Wells et al., Use of comprehensive chromosomal screening for embryo assessment: microarrays and CGH*, 14(12) Molecular Human Reproduction 703 (2008)) at 705 (describing a “widely used ... technique based upon the annealing of semi-degenerate primers” (citing Ex. 12 (*H. Telenius et al., Degenerate oligonucleotide-primed PCR: general amplification of target DNA by a single degenerate primer*, 13(3) Genomics, 718 (July 1992)), Abstract (describing methods of employing “partially degenerate” oligonucleotides)).

For example, the authors of *Molecular Biotechnology: Principles and Applications of Recombinant DNA* (Ex. 13) described a “partially degenerate” sequence as one that contains “a known (fixed) nucleotide at a specific (query) position and any nucleotide in the other positions.” Ehrlich Decl., ¶68 (citing Ex. 13 at 131). Similarly, the authors of the textbook *Human Molecular Genetics* (Ex. 14) defined “partially degenerate ... primers” as “sets of ... sequences that have been synthesized to have the same base at certain nucleotide positions, while differing at other positions.” Ehrlich Decl., ¶68 (citing Ex. 14 at 124). The applicant of U.S. Patent App. No. 11/872,272 (Ex. 15) also used the term “partially degenerate” to describe any “2-” or “3-fold degenerate nucleotide,” wherein 2- and 3- nucleotides were restricted in their nucleotide variability. *Id.* (citing Ex. 15 (U.S. Patent App. Pub. No. 2009/0099040 (Apr. 16, 2009)) at [0005] [0042]).

(ii) Guardant’s proposed constructions improperly import limitations from specific embodiments into the claims.

Guardant’s proposed constructions incorrectly use the term “random.” Guardant has made it clear during the meet and confer on claim construction that it attaches the concepts of known and unknown respectively to the terms “non-random” and “random.” If that is what Guardant intends, the patents’ specifications are clear that degenerate or semi-degenerate sequences can be fully known. *See* Section III.A.4(a)(i).

Whatever Guardant’s intent by using “random” in its proposed constructions, it is not the appropriate word to define the relevant terms. In fact, the patents distinguish between “random” and “degenerate,” *see e.g.*, Ex. 1 at 7:6–8 (“In some embodiments, the SMI tag nucleotide sequence may be completely *random and degenerate*, wherein each sequence position may be any nucleotide”) (emphasis added); Ex. 3 7:14–16 (same); Ex. 4 7:14–16 (same). By describing sequences as being both “random” and “degenerate,” the patents themselves reveal that these

terms are not coextensive, but capture different concepts. Ehrlich Decl., ¶ 72.

The specifications also contradict Guardant’s proposed construction in another important way. For example, the specifications state the degenerate or semi-degenerate SMI sequences may be known and may be specifically “designed,” in one example, to anneal together. Ex. 1 at 13:15–39; Ex. 3 at 13:22–50; Ex. 4 at 13:14–42. As explained by Dr. Ehrlich, skilled artisans would have known that nucleotide sequences *specifically designed* to behave a certain way, such as to anneal, would not be random in most applications Ehrlich Decl., ¶ 64, 65, 72, 73. And, regardless, by the plain language of the specifications they can be *known* and *designed*, and therefore *not exclusively* random. *Id.*

In addition, that the term “random” is mentioned in the specifications but not called out specifically in the claims indicates that the applicant did not wish to narrow the claimed invention in that manner—i.e., if the applicant wanted to specify that a degenerate or semi-sequence must be random, then it knew how to do so. *See Novartis Pharm. Corp. v. Actavis, Inc.*, No. 12-366 (RGA) (CJB), 2013 WL 6142747, at *10 (D. Del. Nov. 21, 2013) (“To the extent that ‘therapeutic treatment’ as used in the specification suggests that ‘treating’ must cause therapeutic improvement, it is significant that the patentees did not choose to modify ‘treating’ in the claims themselves, and the Court will not here import such a limitation from the specification into the claim.”).

In sum, neither the claim language nor the specifications require that the nucleotide bases of the claimed degenerate or semi-degenerate sequences be random, let alone be randomly generated. Accordingly, there is no warrant for reading either limitation into the claims.

(b) Defendant’s Answering Position

TwinStrand’s patents repeatedly and expressly define degeneracy in terms of randomness. Guardant’s constructions are true to this uniform teaching, as well as to the

teaching of other TwinStrand patents and publications and the understanding of a person of ordinary skill in the art (“POSITA”). Plaintiffs’ constructions abandon this clear teaching, deprive degeneracy of its usual meaning, and inject requirements into the claims that are found nowhere in the TwinStrand patents.

(i) Plaintiffs’ constructions improperly broaden the claims and are unsupported by and contrary to the intrinsic evidence

Plaintiffs’ constructions provide that a “degenerate sequence” or a portion of a “semi-degenerate sequence” may be “known or unknown” and also can be totally “unrestricted” with regard to nucleotide “variability.” Under this construction, seemingly any nucleotide sequence is a “degenerate sequence.” Although Plaintiffs clearly wish to expand their claims, this goes too far, rendering the term “degenerate” meaningless. *Pause Tech., LLC v. TiVo, Inc.*, 419 F.3d 1326, 1334 (Fed. Cir. 2005) (“By arguing that the ‘time interval’ can vary after the determination is made and the buffer begins receiving signals, Pause attaches no significance to the word ‘predetermine.’ In construing claims, however, we must give each claim term the respect that it is due.”).

In science and engineering, the term “degenerate” often is used in the context of members of a set of objects to connote a shared characteristic or function among the members of the set. *See, e.g.*, Exs. 39-41. TwinStrand’s constructions, however, include nothing to suggest any unifying characteristic among “degenerate sequences.” Just the opposite, they seemingly permit the “degenerate sequences” in a set to be any sequence whatsoever regardless of whether they have anything in common or behave and function differently. As shown below, Guardant’s constructions give meaning to the term “degenerate” and make clear that “degenerate sequences” are “degenerate” because they all share the characteristic of being “random” as is expressly taught by TwinStrand’s own patents and publications. *See* § III.A.4(b)(ii)-(iii).

Plaintiffs further torture the meaning of “degenerate sequence” by construing it in terms of “variability” notwithstanding the fact that *none* of the TwinStrand patents *ever* refers to “variability” or “variable” to describe degenerate or semi-degenerate sequences. While Plaintiffs rely on an expert declaration to advance their “variability” position (*supra* at 38-39 (citing Ehrlich declaration)), such extrinsic evidence cannot support injecting “variability” into the claims where there is no support in the specifications and where, as here, the specifications instead specifically describe degeneracy in terms of randomness. *See* § III.A.4(b)(iii).

Plaintiffs also fall short by including the phrase “at least one nucleotide position is fixed” in their construction of “semi-degenerate,” which results in that term encompassing a sequence having fixed nucleotides at *every* position. Such an *entirely fixed* sequence is neither a degenerate sequence nor a semi-degenerate sequence. Ex. 20, Quackenbush Decl. ¶ 41.

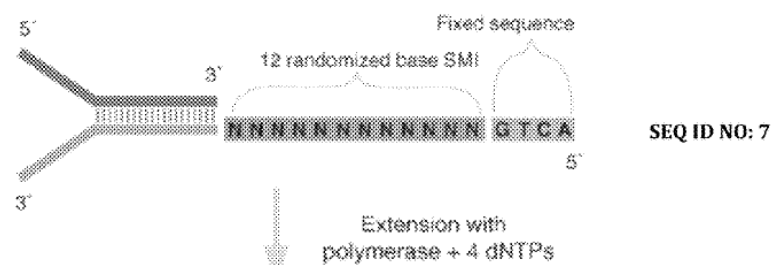
(ii) Guardant’s constructions are fully supported by the intrinsic evidence

While Plaintiffs’ constructions give no meaning to the term “degenerate” and essentially read it out of the claims, Guardant’s constructions vindicate the ordinary meaning of the term and comports with the express teaching of the specifications. TwinStrand’s asserted patents describe using “unique” single molecule identifiers (“SMIs”) to reduce the error rate in DNA sequencing. *See, e.g.*, Ex. 1, ’631 patent at 28:4-51. Importantly, the specifications unambiguously teach that these unique SMIs include “a double-stranded, complementary SMI sequence (or ‘tag’) of 12 *random nucleotides (or a random ‘degenerate sequence’)* per strand.” *Id.* at 22:22-27 (emphasis added). This definitional language clearly equates degeneracy with randomness. *See McCarthan v. Dir. of Goodwill Indus.- Suncoast, Inc.*, 851 F.3d 1076, 1088 (11th Cir. 2017) (“The word ‘or’ commonly introduces a synonym or ‘definitional equivalent.’”). Indeed, the specifications are replete with statements tying degeneracy to randomness. Ex. 1,

'631 patent. at 6:48-63 (“random degenerate sequence”), 6:66-7:2 (“random degenerate nucleotide n-mer sequence”), 7:6-18 (“random and degenerate, wherein each sequence position may be any nucleotide”); 22:28-30 (explaining that the “random” 12-nucleotide sequence will have a “unique 24 nucleotide SMI sequence”). Ex. 20, Quackenbush Decl. ¶¶ 42-44.

The specifications' figures are in accord. Figure 2 of the '631 patent (reproduced below) depicts synthesis of an exemplary SMI adaptor molecule. Ex. 1, '631 patent at 3:63-64.

Figure 2



In the figure, the “*degenerate* lower arm sequence” is represented by “N’s.” *Id.* at 3:63-4:3 (emphasis added). As seen above, this “degenerate lower arm sequence” is labeled “12 *randomized* base SMI”. *Id.* at Fig. 2 (emphasis added). Ex. 20, Quackenbush Decl. ¶ 45.

The uniform descriptions in the text and figures of the specifications distinguish the randomized (*i.e.*, degenerate) SMI from the adjacent “fixed sequence.” *Id.* at 20:46-48 (“SMI adaptors include a 12 nucleotide *random* sequence, followed by a 5 nucleotide *fixed* sequence.”) (emphasis added). This is consistent with the other disclosures in the specifications. *See, e.g.*, *id.* at 12:58-61 (distinguishing an SMI with a “random oligonucleotide sequence” from one with a “set of fixed sequences”), 3:63-4:3 (“Oligonucleotides are annealed and the complement of the degenerate lower arm sequence (N’s) plus adjacent fixed bases is produced by polymerase extension. . .”), 12:58-61 (“The single-stranded SMI sequence tag can be synthesized as a random oligonucleotide sequence, or can be sequenced as a set of fixed sequences. . .”), 21:4-6

(“Discard reads that do not have the 5 nt fixed reference (or “spacer”) sequence (CAGTA; SEQ ID NO: 6) present after 12 random nucleotides.”). These passages further demonstrate that the patents teach that the degenerate (*i.e.*, non-fixed) sequences (or the degenerate portions of semi-degenerate sequences) are generated by randomization. Ex. 20, Quackenbush Decl. ¶ 47.

The TwinStrand patents repeated and uniform characterization of degenerate sequences as being random means that “it is proper to construe the claim term in accordance with that characterization.” *Wis. Alumni Research Found. v. Apple Inc.*, 905 F.3d 1341, 1351 (Fed. Cir. 2018); *see also Profectus Tech. LLC v. Huawei Techs. Co.*, 823 F.3d 1375, 1381 (Fed. Cir. 2016) (affirming construction of “mountable” as “having a feature for mounting” where “every embodiment disclosed in the specification” included a mounting feature). This is especially true where, as here, Plaintiffs “have not pointed . . . to any portion of the specification that describes degenerate SMI sequences as being non-random or fixed.” *Wis. Alumni*, 905 F.3d at 1351; *see also Profectus*, 823 F.3d at 1381. Instead, as explained above, the specification expressly distinguishes between degenerate and fixed sequences. Indeed, the importance that the patents place on using randomly generated SMI sequences to ensure sufficient variation to uniquely tag DNA fragments further supports Guardant’s constructions. *AstraZeneca AB v. Mylan Pharm.*, 19 F.4th 1325, 1330-32 (Fed. Cir. 2021) (rejecting “acontextual read” of claim language that ignored the importance of the construction to the invention).

Although Plaintiffs assert that random and degenerate are “different concepts” (*supra* at 41-42), Plaintiffs fail to explain what that purported difference is in the TwinStrand patents. Indeed, the passages cited by Plaintiffs employ the two words to express a single concept rather than to distinguish between them. *See, e.g.*, Ex. 1, ’631 patent at 7:6-8 (“the SMI tag nucleotide sequence may be completely random and degenerate, wherein each sequence position may be

any nucleotide”); Ex. 20, Quackenbush Decl. ¶¶ 48-49.

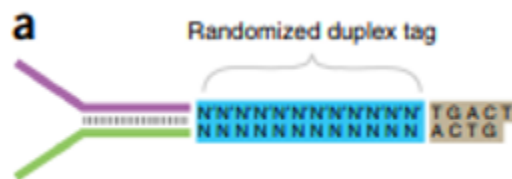
Plaintiffs also argue that the specifications disclose that the SMI sequences may be “designed” and are therefore not random. *Supra* at 42. But the portion of the specification cited by Plaintiffs concerns the design of oligonucleotide adaptors that include SMI sequences, not the design of SMI sequences themselves. The passage states that “[t]he *oligonucleotide* may be designed with appropriate regions of self-complementarity . . .” Ex. 1, ’631 patent at 13:15-24 (emphasis added). The specification consistently uses “design” to refer to the overall design of the adaptor, and not to the SMI sequence. *See, e.g., id.* at 9:16-19 (referring to “design” that “may *include* use of any sequencing adaptor (such as one lacking an n-mer tag) in conjunction with an n-mer tag that is incorporated into the U-shaped linker molecule.”) (emphasis added). Where the SMI sequence in the adaptor (X’s) is “degenerate,” the specification teaches that the complementary bases (Y’s) may be added using a DNA polymerase, which confirms that the degenerate sequence is itself not designed. *Id.* at 9:31-44. Ex. 20, Quackenbush ¶¶ 50-51.

(iii) Guardant’s constructions also are supported by the extrinsic evidence

The extrinsic evidence, including TwinStrand’s own patents and publications, further confirm that degenerate and random are equated. Ex. 20, Quackenbush Decl. ¶¶ 52-53. TwinStrand’s patents and applications directed to Duplex Sequencing (the TwinStrand technology at issue here) define “degenerate” and “semi-degenerate” to mean “random” and “semi-random.” *Id.* at ¶ 53. For example, U.S. Patent No. 11,332,784, titled “Adapters, Methods, and Compositions for Duplex Sequencing,” states that SMIs may be “*random/degenerate, semi-random/semi-degenerate*, or pre-defined.” Ex. 23, ’784 patent at Table 1, Col. 18 (emphasis added); *see also* Ex. 24, ’390 application at [0048], [0076] (defining “*degenerate* SMIs” as “*Random* Unique Molecular Identifiers,” and explaining that during SMI

synthesis, “the template strand can include . . . a region of *random* or *semi-random* nucleotide sequence (e.g., a *degenerate* or *semi-degenerate* sequence).”) (emphasis added).

Dr. Jesse Salk, TwinStrand’s co-founder and a named inventor on the TwinStrand asserted patents, also publicly described TwinStrand’s degenerate SMI sequences as random. The figure below is from a paper on which Dr. Salk was a co-author (“Detecting ultra-low frequency mutations by Duplex Sequencing,” by Kennedy et. al.), which TwinStrand subsequently promoted as describing its technology. Ex. 25, Kennedy 2014. This figure



identifies the 12-nucleotide SMI sequence as a “*Randomized* duplex tag” and describes it elsewhere as a “*random* double-stranded tag.” *Id.* at FIG. 1 (emphasis added).

In the article, Dr. Salk further says the adapters are “constructed by annealing two oligonucleotides, one of which contains a 12-nt [nucleotide] single-stranded *randomized* tag sequence. A DNA polymerase is used to copy *the degenerate* tag sequence, thereby converting it to a double-stranded form.” *Id.* at 2590 (emphasis added). Dr. Salk also says the “[t]welve random nucleotides per adapter (24 nt per final ligated molecule) significantly exceed the degeneracy needed to ensure unique labeling of every molecule in the library.” *Id.* at 2591; see also Jesse Salk, *TwinStrand Biosciences Discusses Duplex Sequencing AACR 2019* (Aug. 4, 2020) at 2:44-3:17min (available at https://www.youtube.com/watch?v=DGSghjqz_GQ) (“the way duplex sequencing works is we have a unique label that is affixed to every single molecule, so in this particular case, those ‘Ns’ represent a random degenerate sequence . . . the top sequence and the bottom sequence (N and N’) just means that there is a complimentary randomized sequence, and in this case there are twelve N’s which means there are 4¹² possible

combinations and if we ligate one of these adaptors on one end and one of the other end we have 4^{24} possible random combinations and there is just simply no way that two molecules have the same label by random chance.”).

As Dr. Salk’s statements recognize, randomization of bases in the SMI sequence is necessary to uniquely tag target molecules. Indeed, if the 12-nucleotide tag was not randomized, it would not be possible to achieve the 4^{12} (or 4^{24} using adaptors on both ends) possible sequences described by Dr. Salk. Ex. 20, Quackenbush Decl. ¶¶ 54-58.

Third party patents in the sequencing adaptor field further confirm that degenerate and semi-degenerate are defined as random and semi-random, respectively. U.S. Patent No. 11,085,084 assigned to Stanford University states that “[t]he term ‘*random sequence*’ is used interchangeably with the term ‘*degenerate sequence*,’ i.e., the sequence not having a precise definition.” Ex 21, ’084 patent at 8:14-16 (emphasis added); *see also* Ex. 22, ’166 patent application by Menarini Silicon Biosystems at 22:7-10 (“By ‘UMI’ or ‘Unique Molecular Identifier sequence’ there is intended *degenerate* or *partially-degenerate* (i.e., *random* or *semi-random*) oligonucleotide sequences which are virtually unique for each ssDNA or dsDNA molecule.”) (emphasis added). Ex. 20, Quackenbush Decl. ¶ 59.

A POSITA also understands that a degenerate sequence is random, and that a semi-degenerate sequence is semi-random. *Id.* at ¶ 60. As Dr. Quackenbush explains, a degenerate sequence consisting of “Ns” means that each N can be *any* of A, T, G, or C (as Plaintiffs acknowledge), not a subset (for example, only A or T). *Id.* This is consistent with the International Union of Pure and Applied Chemistry (“IUPAC”) convention, which provides that “N” in a DNA sequence represents *any* (“aNy”) base, not a subset of bases or an individual base. *Id.*; Ex. 26, NC-IUB, *Nomenclature for incompletely specified bases in nucleic acid sequences*,

Proc. Natl. Acad. Sci. USA 83 (1986) at 5, Table 1.

The references cited by Plaintiffs also are consistent with Guardant’s constructions. For example, the passage cited from *Molecular Biotechnology* states that a “partially degenerate” sequence contains a “known (fixed) nucleotide at a specific (query) position and *any* nucleotide in the other positions.” *Supra* at 41 (emphasis added). This is not inconsistent with the randomization that occurs at the non-fixed positions. The passage cited from *Human Molecular Genetics*, which describes a partially degenerate sequence as one with “the same base at certain nucleotide positions, while differing at other positions” (*id.*), also is consistent with randomization to create “differing” bases at non-fixed positions. Thus, to the extent these extrinsic references touch on variability at non-fixed positions, they are not inconsistent with the express teaching of the TwinStrand patents and publications that equate degeneracy and randomness in the claimed TwinStrand invention. Ex. 20, Quackenbush Decl. ¶¶ 61-62.

(c) Plaintiffs’ Reply Position

In support of its constructions of these terms, Guardant ascribes the same meaning to two terms: “degenerate” and “random.” Guardant argues that a degenerate sequence is randomly generated without *a priori* knowledge of which nucleotides exist at each position. But, in equating “degenerate” with “random,” Guardant improperly imports limitations from the specifications into the claims, while excluding embodiments from the specifications.

Guardant presses for this unreasonable construction for purely litigation-driven reasons: as Guardant admits, its own accused products use non-random sequences; that is, the order of nucleotides in the sequence is known. *See* Guardant Tech Tutorial at 11:29–35. To avoid infringement, Guardant urges the Court to construe “degenerate” to mean a randomly generated sequence, thus improperly trying to shoehorn a non-infringement argument into its construction.

As explained in Plaintiffs’ opening brief, in a degenerate sequence, any nucleotide can be

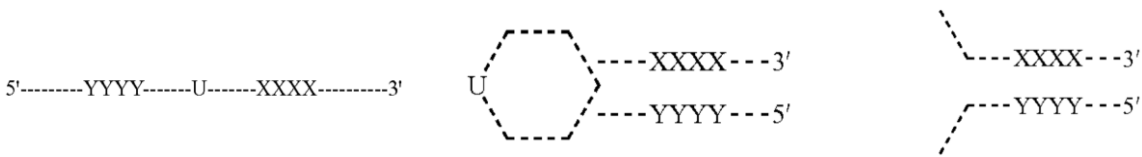
at any particular nucleotide position in that sequence, whether that nucleotide is randomly generated or not, or designed or not. Guardant’s expert agrees with the basic definition of a degenerate sequence stating a “*degenerate* lower arm sequence” consisting of “Ns” means that each N can be any of A, T, G, or C not a subset (for example, only A or T). Ex. 20, Quackenbush Dec. ¶ 45. As Dr. Ehrlich explains, degenerate sequences can be designed and known. Ex. 42, Ehrlich Reply Dec. ¶¶ 74–78. The patent specifications supports this understanding and describe both randomly generated and designed and known barcode sequences.¹⁶ *Id.*, ¶¶ 79–87.

(i) The specifications disclose designed degenerate sequences, which would be excluded under Guardant’s proposed constructions.

Guardant’s construction of “degenerate” would exclude all embodiments in the patent where the degenerate sequence was non-random or known. *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1305 (Fed. Cir. 2007) (“We normally do not interpret claim terms in a way that excludes disclosed examples in the specification.”). The specification discloses such embodiments and Guardant’s argument (at 46) that Plaintiffs have not pointed to embodiments that describe degenerate SMI sequences as being non-random or fixed is false.

As Plaintiffs point out in their opening brief (at 40), the ’631 patent at 13:15–22, describes a degenerate single molecule identifier (SMI sequence) that can be known or designed. For example, the specification describes molecular-identifier sequences included in a set of single-stranded, linear oligonucleotides, depicted below, “*designed* with appropriate regions of self-complementarity to anneal.” Ex. 1, ’631 patent, 13:15–33 (emphasis added).

¹⁶ Much of the evidence cited by Guardant (at 42–50) shows (in its view) that “degenerate” is “*consistent*” with “random.” But both sides agree that degenerate sequences *may* be random, so it is unremarkable that there is evidence showing these terms are not in conflict. This fact does not shed light on the critical question whether “degenerate” *must* mean “random.”



Guardant does not dispute (at 45–47) that the X’s and Y’s shown in these schematics depict degenerate SMI sequences. But, despite the fact that the specification expressly states that the oligonucleotides may be “designed,” Guardant disputes that the schematic shows a designed degenerate sequence, *i.e.*, a degenerate sequence having a known sequence. *First*, Guardant claims (at 47) that this section of the specification “concerns the design of oligonucleotide adaptors that include SMI sequences, not the design of SMI sequences themselves.” That statement is nonsensical and is contrary to the express teaching of the specification. The specification states that the embodiment described above is that of a “SMI adaptor molecule.” Ex. 1, ‘631 patent, 13:2–10. Then it states, “SMI adapter molecules containing a double-stranded complementary, *degenerate or semi-degenerate SMI tag* can be made by any of a number of methods.” *Id.* at 12:64-66. And, finally, “[f]or example, a set of nucleotides of *known* sequence where *X and Y represent the complementary SMI sequences* can be synthesized on an array, or by any other suitable method known in the art.” *Id.* at 13:36–39. That is, the specification expressly states that for this embodiment, X and Y represent a degenerate SMI sequence where the nucleotides in the sequence are known. Ex. 42, Ehrlich Reply Dec. ¶¶ 82–83. Even Guardant’s expert agrees that this degenerate sequence is known, and testified that the X’s and Y’s in the above schematic must be known “*a priori*” in order to properly anneal. Ex. 44, Quackenbush Tr. at 176:7–177:14.

Tellingly, in arguing that the specifications use the term “design” to refer to the overall design of the adapter and not the SMI sequence, Guardant cites a *different* part of the

specification describing a different embodiment. *See* Def. Br. at 47 (citing Ex. 1 at 9:16–19).

And Guardant’s second argument, that the specification teaches that degenerate bases are not designed, cites to yet another embodiment. *Id.* (citing Ex. 1 at 9:31–44).

Further, there are several instances in the specification where the terms “degenerate” and “semi-degenerate” appear without any mention of randomness. *See, e.g.*, Ex. 1, ’631 patent, 3:1–9, 3:63–4:1, 6:48–51, 6:54–66, 7:22–27, 9:11–16, 9:30–36, 10:66–11:3, 12:64–13:2, 16:33–38. Elsewhere, the specification describes “[t]he degenerate or semi-degenerate n-mer sequences may be generated by a polymerase-mediated method described in the Example below, or may be generated by preparing and annealing a library of individual oligonucleotides of *known sequence*.” Ex. 1, ’631 Patent, 7:23–27 (emphasis added); *see also*, Ex. 9, Ehrlich Dec. ¶ 64. Guardant’s constructions would exclude these embodiments.

Guardant’s attempts (at 45–46) to distinguish “randomized” molecular identifiers from “adjacent ‘fixed sequences’” backfires for the same reason—one of the excerpts that Guardant cites discloses other embodiments of fixed or known degenerate sequences that would be excluded by Guardant’s constructions. In particular, Guardant quotes (at 45) the following: “[t]he single-stranded SMI sequence tag can be synthesized ... as a set of fixed sequences ... on an array,” Ex. 1, ’631 patent, 12:58–61. Indeed, this description is the opposite of “randomly generating” nucleotide sequences. This embodiment supports Plaintiffs’ constructions because synthesizing “a set of fixed sequences” could be done in a degenerate sequence because every nucleotide position is unrestricted in its nucleotide variability. Ex. 42, Ehrlich Reply Dec. ¶ 89.

(ii) The specifications treat “random” and “degenerate” as different terms and Guardant’s definition improperly imports a limitation from the specification.

Guardant’s construction that “degenerate” means “random” imports a limitation from the specification into the claims and excludes other described embodiments. This is improper. *See*

Phillips v. AWH Corp., 415 F.3d 1303, 1320 (Fed. Cir. 2005) (“[O]ne of the cardinal sins of patent law—reading a limitation from the written description into the claims.”). That the term “random” is mentioned in the specifications but not explicitly used in the claim indicates that the patentee did not wish to narrow the claimed invention in that manner. *See Novartis Pharm. Corp. v. Actavis, Inc.*, No. 12-366, 2013 WL 6142747, at *10 (D. Del. Nov. 21, 2013) (“To the extent that ‘therapeutic treatment’ as used in the specification suggests that ‘treating’ must cause therapeutic improvement, it is significant that the patentees did not choose to modify ‘treating’ in the claims themselves, and the Court will not here import such a limitation ... into the claim.”).

Notably, Guardant’s claim (at 42) that Plaintiffs’ patents “repeatedly and expressly define degeneracy in terms of randomness” is false. In fact, each section of the specifications that Guardant cites actually supports Plaintiffs’ position that the terms are different.

For example, Guardant (at 44–45) argues that the ’631 patent (Ex. 1 at 22:26–27) defines degeneracy as randomness where it describes a molecular identifier sequence as “12 random nucleotides (or a random ‘degenerate sequence’).” This, Guardant argues, is where the specification “equates degeneracy with randomness” because the word “or” “commonly introduces a synonym or ‘definition equivalent.’” *Id.* But, a more natural reading of the language is that the specification is equating the words “12 *random* nucleotides” with “a *random* ‘degenerate sequence,’” *i.e.*, is equating the nucleotide sequence that is 12 bases in length with a degenerate sequence. If the specification had intended to treat the terms random and degenerate as the same, then there would be no reason to modify “degenerate” with *random*, *i.e.*, the specification would simply have said “12 random nucleotides” or “degenerate sequence.”

Every other instance that Guardant cites in its brief (at 44–45) also uses both “random” and “degenerate” as descriptors. Indeed, as explained in Plaintiffs’ opening brief (at 41–42), the

specifications expressly state that degenerate sequences *can be* random. *See, e.g.*, Ex. 1, '631 patent, 7:6–8 (“In some embodiments, the SMI tag nucleotide sequence may be completely random *and* degenerate, wherein each sequence position may be any nucleotide.”) (emphasis added); *id.* at 6:51–53 (“In *some* embodiments, the degenerate or semi-degenerate SMI sequence *may be* a random degenerate or semi-degenerate sequence.”) (emphasis added); *see also Baxalta Inc. v. Genentech, Inc.*, 972 F.3d 1341, 1349 (Fed. Cir. 2020) (“[T]he written description’s use of ‘may also include,’ ‘e.g.,’ ‘such as,’ and ‘etc.’ makes clear the patentee did not intend this excerpt of the written description to define” the disputed term.). It is difficult to see how Guardant can claim (at 46) that describing a nucleotide sequence as “random” *and* “degenerate” is using “two words to express a single concept.”

The *Wisconsin Alumni* and *Profectus* cases Guardant’s cites (at 46) as support do not stand for the proposition that Guardant claims. The courts in those cases did not adopt constructions simply because they were in accordance with how the feature was often described in the specifications. Rather, in both cases, the Court rejected constructions because they were beyond “anything described” or “contemplated” in the specifications. *Wisconsin Alumni*, 905 F.3d at 1352; *Profectus*, 823 F.3d at 1381. Regardless, as explained above, the patent specifications do not characterize “degenerate” as “random.

The specifications do not deviate from showing degenerate sequences as sequences where the nucleotide position may be any nucleotide. *See, e.g.*, Ex. 1, '631 patent, 9:31–44 (showing a hairpin oligonucleotide “where X’s represent degenerate nucleotides”); *id.* at 10:36–38 (“sequences can thus be identified by virtue of having matching SMIs of the form XXXX in Read 1 and XXXX in Read 2”); *id.* at 13:36–38 (“a set of nucleotides of known sequence where X and Y represent the complementary SMI sequences can be synthesized on an array”).

Guardant’s arguments that the specification treat “degenerate” and “random” as the same fail.

(iii) Guardant’s remaining arguments are similarly unavailing.

Guardant states (at 44) that the term “variable” is improper because the specifications do not *explicitly* use it to describe degenerate sequences. Yet, Guardant’s term “randomly generated” is also entirely absent from the specifications. In addition, Guardant’s argument (at 43) that the term “degenerate” is used to connote a shared characteristic or function among the members of the set merely cites to three references without any explanation. And, anyway, in Plaintiffs’ patents, the claimed degenerate or semi-degenerate sequences SMI all have a shared characteristic—they are molecular identifiers, which are used to differentiate molecules.

Guardant incorrectly suggests (at 46) that the claimed inventions require the use of “randomly generated SMI sequences to ensure sufficient variation to uniquely tag DNA fragments.” They do not. Designed sequences, known sequences, and non-random sequences can uniquely label DNA fragments in the claimed methods. Ex. 42, Ehrlich Reply Dec. ¶ 88. Moreover, the claimed inventions do not rely exclusively on the use of unique tags, as Guardant readily recognizes. *See* Def. Br. at 63 (“The patents teach ... [the use of] fragment ends ... in conjunction with SMI tags to uniquely label the target sequence”).

(iv) The extrinsic evidence does not support Guardant’s arguments.

Guardant cites a litany of extrinsic evidence that is in accord with Plaintiffs’ constructions. Dr. Salk’s use of “random” to describe an example of a degenerate sequence in a presentation and interview years after the priority date of the patents, is consistent with Plaintiffs’ constructions. Ex. 42, Ehrlich Reply Dec. ¶¶ 92–98. Plaintiffs do not dispute that a degenerate sequence *may* be random—the issue is whether degenerate sequences *must* be randomly generated as Guardant proposes.

The remaining extrinsic evidence cited in Guardant’s brief (at 47–49) are a set of unrelated patents, including some *third-party* patents. Under well-settled legal principles, such extrinsic evidence has little, if any, bearing on the construction of “degenerate” in this case. *See e.Digital Corp. v. Futurewei Techs., Inc.*, 772 F.3d 723, 727 (Fed. Cir. 2014) (“These distinctions reinforce the well-understood notion that claims of unrelated patents must be construed separately.”). And such evidence cannot overcome the weight of intrinsic and relevant extrinsic evidence supporting Plaintiffs’ constructions. Ex. 42, Ehrlich Reply Dec. ¶ 100.

(d) Defendant’s Sur-Reply Position

Plaintiffs’ argument that “degenerate” sequences are not limited to randomly generated sequences blurs claim boundaries, mischaracterizes the intrinsic record, and reads “degenerate” out of the claims. While Plaintiffs agree that “degenerate” and “semi-degenerate” can mean “random” and “semi-random” in the context of their patents, *supra* at 51 n.16, they argue that “in a degenerate sequence, any nucleotide can be at any particular nucleotide position . . . , whether that nucleotide is randomly generated or not, or designed or not,” or known or unknown. *Id.* at 50-51. Under Plaintiffs’ interpretation, even “fixed sequences” can be “degenerate,” extinguishing the sole distinction between Plaintiffs’ construction for “degenerate” and “semi-degenerate.” *Id.* at 53. This is improper. *Pause Tech.*, 419 F.3d at 1334 (rejecting claim construction that rendered claim term meaningless).

(i) Guardant’s constructions are supported by the intrinsic evidence

Context is the key to claim construction. *Phillips*, 415 F.3d at 1315. The specifications focus on unique tagging, and randomization ensures the diversity of sequences necessary for unique tagging. Ex. 20, Quackenbush Decl. ¶ 42; Ex. 9, Ehrlich Decl. ¶ 44. The specifications further equate degeneracy with randomness, teaching that unique SMIs include a tag “of 12

random nucleotides (or a *random ‘degenerate sequence’*) per strand.” Ex. 1, ’631 patent 22:22-27. Plaintiffs argue that the “natural reading” of this language is that “degenerate sequence” just means any 12 nucleotides. But this gives no meaning to “degenerate” if a degenerate sequence can be any sequence, no matter how generated.

Figure 2 in the specification refers to the pictured SMI sequence as a “12 *randomized* base SMI.” That SMI sequence is described in the specification as the “*degenerate* lower arm sequence.” *Id.* 3:63-4:3. Plaintiffs fail to meaningfully address this disclosure. The specification also explains that an SMI tag may be “*completely* random and degenerate” such that “each sequence position may be any nucleotide.” *Id.* 7:6-8. This is in contrast with an SMI tag that is semi-degenerate, which would not be “completely” random. The specifications further state: “In some embodiments the degenerate or semi-degenerate SMI sequence may be a *random* degenerate sequence.” *Id.* 6:51-53. Thus, where embodiments use a degenerate sequence (as opposed to a semi-degenerate sequence), that sequence is random. It does not indicate that the degenerate sequence “may be” random. Plaintiffs misquote this passage, adding the phrase “or semi-degenerate sequence” to the end of the sentence. *Supra* at 55. Whether this suggests that a degenerate sequence “may be” random is irrelevant—it is not in the specification.

Guardant’s constructions do not exclude embodiments because *there are no embodiments* disclosed in which a “degenerate” SMI sequence is expressly non-random or fixed. Plaintiffs fixate on the “design” of an adapter oligonucleotide with an SMI sequence. The specification, however, discloses that in this example “[t]he *oligonucleotide* [adapter or precursor] may be designed with appropriate regions of self-complementarity.” Ex. 1, ’631 patent 13:15-24. Plaintiffs acknowledge that the focus of the design is the SMI adaptor molecule “containing” the SMI sequence, not the SMI sequence itself. *Supra* at 52; Ex. 1, Fig. 2

(synthesis of an adaptor *containing* a degenerate SMI sequence denoted as a “12 *randomized* base SMI.”). The other embodiments supposedly excluded by Guardant’s construction are also not expressly degenerate sequences. Column 12 describes a “single-stranded SMI sequence tag,” not a *degenerate* SMI sequence. Ex. 1, ’631 patent 12:58-61.

In *Wisconsin Alumni* and *Profectus*, the Federal Circuit adopted constructions consistent with the repeated and consistent disclosures in the specification. *Wis. Alumni*, 905 F.3d at 1351 (“Where, as here, a ‘patent ‘repeatedly and consistently’ characterizes a claim term in a particular way, it is proper to construe the claim term in accordance with that characterization.”); *Profectus*, 823 F.3d at 1381 (“the specification does not disclose a bare embodiment in which the picture display or picture frame lacks a feature for mounting.”). The court rejected competing constructions because they did not appropriately confine the scope of the claims to the disclosures of the specification. *Wis. Alumni*, 905 F.3d at 1351-52 (proposed construction would “expand the scope of the claims far beyond anything described in the patent”); *Profectus*, 823 F.3d at 1380.

Plaintiffs are also wrong that the specifications disclose a “designed” or “known” degenerate SMI sequence. The patent never states that the SMI sequence used in this example is degenerate. Ex. 1, ’631 patent 13:2-33. Nor does it state that the SMI sequence in this “designed” example is “known”—the language cited by Plaintiffs for that proposition is discussing another embodiment (also not expressly degenerate). *Id.* 13:34-39. Contrary to Plaintiffs’ assertion, Guardant’s expert did not testify that this was a degenerate sequence or that it was known. *Supra* at 52. Instead, he confirmed that the SMI portions of the oligonucleotide adaptors are “randomly inserted in the process of oligo synthesis” and explained that in his view the figure “doesn’t actually show the SMI tag itself, which we know from the patent is a random

collection or a random set of oligonucleotides.” Ex. 44, Quackenbush Tr. 177:15-178:13.

Further, the fact that degenerate sequences can be generated by “copying of a single-stranded SMI sequence by a DNA polymerase” (Ex. 1, ’631 patent 3:64-4:1, 9:30-36) does not mean that the degenerate sequence is *a priori* “designed and known.” One might know what the Powerball number sequence is after the balls are drawn, but that does not change the fact that the numbers were randomly generated. Plaintiffs have failed to point to any intrinsic evidence that does not support Guardant’s construction that a “degenerate sequence” is randomly generated.

(ii) Guardant’s constructions are supported by the extrinsic evidence

Dr. Salk’s paper and presentation demonstrate that the key to DCS is randomization sufficient to create a unique tag for each original DNA fragment. From the time the patents were filed, Dr. Salk has consistently held the view that the random generation of degenerate sequences was important. Ex. 1, ’631 patent 6:66-7:5. Plaintiffs do not identify any contrary teachings. Moreover, the cited TwinStrand patents, which Plaintiffs do not dispute are directed to DCS (the same technology at issue here), also plainly define degenerate and semi-degenerate SMIs as random and semi-random, respectively. This evidence further supports Guardant’s construction.

5. “fragment ends”

Claim Term	Patent, Claim	Plaintiffs’ Proposed Construction	Defendant’s Proposed Construction
“fragment ends”	’631 patent, claim 1	Plain and ordinary meaning	Each fragment end is made up of fewer nucleotides than the entire fragment at the terminal end of the fragment after shearing and trimming

(a) Plaintiffs’ Opening Position

There is no need for the Court to construe the term “fragment ends.” In the claims, “fragment ends” appears as part of the larger phrase “nucleic acid fragment ends.” Nucleic acids

are strands, and so fragments of nucleic acids are portions of those strands. Guardant agrees that the term “fragment” is sufficiently clear as to not warrant any construction by the Court—after all, Guardant’s proposed construction of “fragment ends” uses the term “fragment” as part of it.¹⁷ Given that, the entire term “fragment ends” has a straightforward meaning that any layperson can understand—the distal or terminal parts of the fragment. Ehrlich Decl., ¶¶ 77–85; *see also Extang Corp. Undercover, Inc. v. Truck Accessories Grp., LLC*, No. CV 19-923 (MN), 2020 WL 6888277, at *7 (D. Del. Nov. 24, 2020) (finding that “a well-known term to a person of ordinary skill in the art” does not require any construction and should “have its plain and ordinary meaning”). Construction of this term is unnecessary.

In asking the Court to define “fragment ends,” Guardant is not seeking a definition that will illuminate the meaning of the term for the Court or the jury, but rather to lard the term with additional requirements so it can make non-infringement arguments later in the case. In particular, Guardant’s proposed construction imports two limitations into the claims. Both are improper. *See Intel Corp. v. Int’l Trade Comm’n*, 946 F.2d 821, 836 (Fed. Cir. 1991); *see also Cadence Pharm. Inc. v. Exela PharmSci Inc.*, 780 F.3d 1364, 1369 (Fed. Cir. 2015) (“[E]ven if all of the embodiments discussed in the patent include[] a specific limitation, it would not be proper to import from the patent’s written description limitations that are not found in the claims themselves.”) (quotation marks and citation omitted).

Guardant’s proposed construction attempts to limit the relevant fragment to what remains “after shearing and trimming.” But there is no basis, in the claims or in the intrinsic record, to require this. Ehrlich Decl., ¶¶ 81–83. While it is true that the patents encompass shearing and

¹⁷ Relatedly, because Guardant does not propose a construction of “fragment,” it appears that it does not believe the jury will have any difficulty understanding that term or would otherwise benefit from the Court construing it. Plaintiffs agree.

trimming, the patents do not describe that these steps are always part of the claimed invention.

Cont'l Circuits, 915 F.3d at 797–98. And the claims do not contain any language requiring these steps.

The Court should reject Guardant's attempt to import these limitations into the claims and should instead apply the plain and ordinary meaning of "fragment ends."

(b) Defendant's Answering Position

Plaintiffs agree that "fragment ends" include "the distal or terminal parts of the fragment." *Supra* at 61. Thus, there does not appear to be a dispute that the "fragment ends" are "made up of fewer nucleotides than the entire fragment" and are found "at the terminal end of the fragment" as set forth in Guardant's construction. The sole focus of the parties' dispute is therefore whether the claimed "fragment ends" require shearing and trimming as set forth in Guardant's construction.

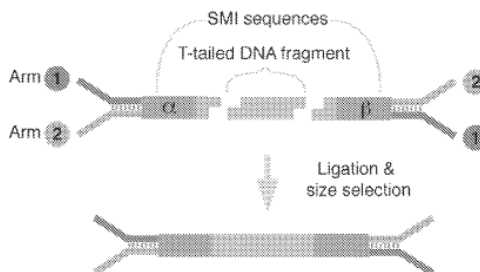
The TwinStrand patent methods depend on the generation of "a sufficiently large number of unique tags to label a set of sheared DNA fragments from a segment of DNA." Ex. 1, '631 patent at 6:59-63. This "allows every molecule to be uniquely labeled prior to PCR duplication." *Id.* at 18:42-47. As the above passages suggest, these DNA fragments are created by shearing of larger DNA molecules. *Id.* at 19:64-20:1 ("DNA . . . was sheared on the Covaris AFA system"); *id.* at 22:48-50 (target DNA is "sheared and end-repaired by standard methods, with size-selection for fragments in the range of ~200-500 [base pairs]."). The specification also discloses shearing using a restriction endonuclease. *Id.* at 14:12-18; Ex. 20, Quackenbush Decl. ¶ 65.

Adaptors containing SMI sequences are then ligated to the fragment ends. *See, e.g.*, Ex. 1, '631 patent at 3:44-53 ("Sheared double-stranded DNA that has been end-repaired and T-tailed is combined with A-tailed SMI adaptors"), 15:10-15 ("The sheared target DNA or RNA molecule may be end repaired and a double-stranded target nucleic acid sequence ligation

adaptor may be added to each end of the sheared target DNA or RNA molecule.”), 21:2-24.

Figure 1 illustrates the ligation of SMI-containing adapters to the ends of the sheared fragment in the middle:

Figure 1



The patents teach that the fragment ends play a role in unique labeling. For example, the fragment ends are used in conjunction with SMI tags to uniquely label the target sequence. Ex. 1, '631 patent at cl. 1 (SMI sequence “alone or in combination with the target nucleic acid fragment ends uniquely labels each ligated double-stranded target nucleic acid molecule”); *id.* at 9:11-15 (combination of “sheared ends” and n-mer tag “may also serve as unique molecular identifiers.”). In addition to being used in conjunction with tags, the sheared ends of the fragments may themselves be used “as identifiers to differentiate unique individual molecules.” *Id.* at 9:3-6; *see also id.* at 17:46-50 (“the sequencing method may be performed . . . without the use of SMI adaptor molecules, but instead by using the random shear points of DNA as identifiers.”), 26:24-28 (“the randomly sheared DNA ends were used as SMI’s.”), 18:42-49, 23:39-46. The patents further teach that the four nucleotides after the SMI adaptor sequence at the end of each fragment should be trimmed (*i.e.*, removed) prior to grouping to reduce the error rate. *Id.* at 20:53-56; 21:13-14.

Because the specification does not disclose any method of generating fragments other than shearing, and because shearing is an integral part of creating sufficient variability in the fragment end sequences to permit unique labeling or tagging, a POSITA would understand that

fragment ends, as used in claim 1, are the result of shearing. Ex. 20, Quackenbush Decl. ¶¶ 66-70.

(c) Plaintiffs' Reply Position

Guardant misconstrues “fragment ends” in claim 1 of the '631 patent, proposing a construction that imports the independent concepts of “shearing and trimming” into the claims.

Regarding “shearing”: Guardant argues (at 64) that these concepts should be included in “fragment ends” because “the specification does not disclose any method of generating fragments other than shearing” and “shearing is an integral part of creating sufficient variability.” Both statements are incorrect and, regardless, neither justifies Guardant’s construction.

First, the specifications explicitly articulate methods of generating fragments without shearing. The specifications teach that in some embodiments, fragments can be generated using polymerase chain reactions (PCR), which was and remains a well-known method for amplifying copies of specific segments (i.e., fragments) of nucleic acid molecules *without shearing*. Ex. 42, Ehrlich Reply Decl. ¶¶ 101–104 (citing Ex. 1 at 14:5–9). During his deposition, Dr. Quackenbush admitted that the '631 patent “allow[s for] other methods” of generating fragments that do not require shearing and that “one skilled in the art would understand that there are other methods.” Ex. 44, Quackenbush Tr. 58:8–11, 63:10–14. *See also id.* at 77:20–78:10 (“[s]o what the breadth and scope of methods use to generate those fragments might ultimately be, I don't know), 63:15–17 (“fragmentation, whether it's shearing or any other approach, in fact is necessary to create these fragment ends.”). And even if Guardant’s characterization of the specifications is correct, it would still be improper to read the concept of shearing into the claims because “[a] patent that discloses only one embodiment is not necessarily limited to that embodiment.” *GE Lighting Sols., LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1309 (Fed. Cir. 2014).

Second, shearing is not “an integral part of creating sufficient variability in the fragment end” as Guardant claims (at 64)—the claim itself does not require the use of fragment ends to identify target molecules. Ex. 1, ’631 patent, claim 1; Ex. 42, Ehrlich Reply Decl. ¶¶ 105, 106. Indeed, in a different section of the brief, Guardant argues (at 62) that the claims “depend on the generation of a ‘sufficiently large number of unique tags’” to identify target molecules. Thus, Guardant contradicts its attempt to read into the claims the concept of shearing.

Regarding “trimming”: Guardant’s sole reason (at 64) for incorporating this limitation is that the specifications teach trimming can “reduce the error rate.” That is not a sufficient reason; merely describing the benefits of an embodiment does not limit the scope of the claims. *Honeywell Inc. v. Victor Co. of Japan*, 298 F.3d 1317, 1326 (Fed. Cir. 2002). Guardant does not cite to any support that the claimed fragment ends *must* be trimmed, and its expert does not even discuss trimming in his declaration. *See* Ex. 20, Quackenbush Dec. ¶¶ 65–71. Indeed, Dr. Quackenbush admitted that fragment ends exist before trimming, contradicting Guardant’s construction that the claimed fragment ends exist *only after* trimming. Ex. 44, Quackenbush Tr. 29:16–20, 31:11–14, 71:14–15, 86:5–8. Guardant’s proposed construction should be rejected. Ex. 42, Ehrlich Reply Decl. ¶¶ 107–110.

(d) Defendant’s Sur-Reply Position

Plaintiffs assert that the patents disclose “generating fragments without shearing.” *Supra* at 64. But the cited passage states that “specific PCR primers can selectively amplify specific regions of genome,” not that selective amplification gives rise to fragment ends that can be used in a method to *uniquely* identify the fragments, as required by the claims. Dr. Ehrlich acknowledges that the patents use sheared fragments in the claimed methods (although his analysis is incorrect for other reasons, as set forth herein). *See* Ex. 42, Ehrlich Decl. ¶¶ 21, 23, 24, 27.

Dr. Quackenbush’s testimony is consistent with the intrinsic evidence and his declaration: shearing is required and may be accomplished in multiple ways. Ex. 20, Quackenbush Decl. ¶ 65 (describing “fragmentation” which can be added to Guardant’s construction.) Claim 1 includes the use of the fragment ends in conjunction with an SMI tag to create a unique identifier, which would not be possible without sufficient diversity in the fragment ends. *Id.* ¶ 70. That the claim permits unique tagging using an SMI or an SMI together with the fragment ends is irrelevant—if the diversity of break points is insufficient, SMI plus fragment end tagging may not work.

Regarding trimming, Plaintiffs misconstrue the process of sequencing. Trimming occurs computationally after sequencing, so the *physical* fragment ends exist before *and* after trimming. Ex. 44, Quackenbush Tr. 70:17-71:15; 82:19-83:1; 85:10-11; Ex. 1, ’631 patent 21:2-14. The computational “trimming” occurs in the post-sequencing “data processing workflow” *before* the “grouping” step in which sequence reads are grouped into families based on the SMI sequence and the fragment ends. Ex. 1, ’631 patent 21:2-14. Thus, in the *only* sense that matters for the claim (*i.e.*, post-sequencing computational analysis), “fragment ends” usable in the claimed method do not exist until computational trimming occurs, consistent with Guardant’s construction.

B. Disputed Terms in Defendants’ Patents

1. “comprises between 1 nanogram (ng) and 100 ng of cfDNA molecules”

Claim Term	Patent, Claim	Plaintiffs’ Proposed Construction	Defendant’s Proposed Construction
“comprises between 1 nanogram (ng) and 100 ng of cfDNA molecules”	’221 patent, claim 3 ’306 patent, claim 19	1 ng or greater of cfDNA molecules	Plain and ordinary meaning

(a) Plaintiffs' Opening Position

On the 1-ng-to-100 ng term, the parties' dispute is not one about the disclosure or even about the claimed technology. Rather, the parties dispute the meaning of "comprises" within the claims. Guardant drafted its claims using the term "comprises" in claim 3 of the '221 patent and claim 19 of the '306 patent and the claims must be construed accordingly.

It is well-settled law that the word "comprises" or "comprising" in a claim means "that the listed elements ... are essential but other elements may be added." *Lucent Tech., Inc. v. Gateway, Inc.*, 525 F.3d 1200, 1214 (Fed. Cir. 2008) (collecting cases); *see also Amgen Inc. v. Amneal Pharm. LLC*, 945 F.3d 1368, 1378–79 ("The term 'comprising' is...used to make clear that the claim does not preclude the presence of components or steps that are in addition to, though not inconsistent with, those recited in the limitations that follow."). Therefore, Guardant's choice to recite "comprises between 1 nanogram (ng) and 100 ng" resulted in a claim scope of 1 ng and *all masses* above 1 ng. Consider, for example, a 500 ng sample of cfDNA. Despite exceeding 100 ng, a 500 ng sample nevertheless "comprises" 50 ng, and so falls within the scope of the claim.

This straightforward logic not only comports with the settled meaning of "comprises" but easily squares with other claim-construction principles. These limitations appear in dependent claims and, presumably therefore, narrow the claims from which they depend. *See e.g.*, Ex. 7 ('221 patent) 16:64–65; Ex. 8 ('306 patent) 16:60–61 ("A sample can comprise various amount of nucleic acid that contains genome equivalents."). These independent claims have no limitations with respect to the sample mass of cfDNA. Construing the claims as Plaintiffs propose narrows the independent claims by virtue of excluding masses below 1 ng in the dependent claims, which carries forward the presumption that dependent claims narrow the independent claims from which they depend.

The Court should construe the 1-ng-to-100-ng term consistent with its only reasonable interpretation: “1 ng or greater of cfDNA molecules.”

(b) Defendant’s Answering Position

The term “comprises between 1 nanogram (ng) and 100 ng of cfDNA molecules” is unambiguous and requires no construction. Plaintiffs’ proposed construction is incorrect because it abrogates the clearly recited numeric nanogram range of the claimed cfDNA molecules.

First, the Federal Circuit has flatly rejected the argument that using the term “comprises” somehow erases an otherwise precisely claimed numeric range and instead allows the claim to encompass an amount that exceeds the claimed range. Just as Plaintiffs are arguing here, the plaintiff in *Jeneric/Pentron, Inc. v. Dillon Co.*, 205 F.3d 1377 (Fed. Cir. 2000) cited the use of “comprising” in the claims and “argue[d] that a portion of cerium oxide in the claimed range falls within the literal limits while the remaining portion merely adds to the allegedly infringing matrix.” *Id.* at 1382. The Federal Circuit rejected that argument, finding that the “argument fails because it would read out of claim 1 the express claim ranges.” *Id.* at 1383; *see also id.* at 1381-82 (construing claims to be limited to the recited ranges). This Court should likewise reject Plaintiffs’ attempt to effectively erase the upper “100 ng” end of the claimed range. *See also Wis. Alumni*, 905 F.3d at 1348 n.8 (“But ‘[c]omprising’ is not a weasel word with which to abrogate claim limitations.”) (quoting *Spectrum Int’l, Inc. v. Sterilite Corp.*, 164 F.3d 1372, 1380 (Fed. Cir. 1998)); *Ideal Instruments, Inc. v. Rivard Instruments, Inc.*, 498 F. Supp. 2d 1131, 1163 (N.D. Iowa 2007) (“[T]he specified minimum and maximum values for the weight percentages of certain elements comprising the ‘stainless steel’ in the ‘668 patent ‘represent the outermost bounds of the disclosed embodiments.’ . . . This is particularly true when *Jeneric/Pentron* settled the reading of a list of elements ‘comprising’ a composition, identified

by weight percentage ranges, as specifying precise value ranges for the elements ‘comprising’ the composition.”) (quoting *Jeneric/Pentron*, 205 F.3d. at 1382).

Plaintiffs’ discussion of the “well settled law” regarding “comprises” is not only wrong as it applies to numeric ranges, it also is materially incomplete. Specifically, in *Amgen Inc. v. Amneal Pharms. LLC*, 945 F.3d 1368 (Fed. Cir. 2020), the Court stated that any additional components or steps ***may not be “inconsistent”*** with the claim limitation. *Id.* at 1379. Thus, while the Court found that the use of “comprising” permitted the use of additional unclaimed *ingredients*, the Court did *not* allow the parties to abrogate the recited *numeric range* limitations imposed on those claimed ingredients. In fact, the Federal Circuit remanded the case to the district court to determine if the claimed ingredients were within the claimed ranges in the accused products. *Id.* at 1379-80.

The other case cited by Plaintiffs, *Lucent Tech., Inc. v. Gateway, Inc.*, 525 F.3d 1200 (Fed. Cir. 2008), also provides no support for their position. That case merely stands for the proposition that it is generally presumed that a “comprising” method claim does not preclude the presence of additional unclaimed method *steps*; nothing in that case suggests that expressly recited numeric ranges in a claim can be exceeded. *Id.* at 1214.

Second, there is no language in the Guardant patent claims that otherwise broadens the claimed range. For example, both *Jeneric/Pentron* and *Ideal* cite to “about” as a broadening word that potentially may permit a claim to encompass values beyond the stated numeric range. *Jeneric/Pentron*, 205 F.3d at 1381; *Ideal*, 498 F. Supp 2d at 1162-1663. Here, the claims do not include “about” or any other comparable broadening language.

Third, the dependent claims of the ’221 patent further support Guardant’s construction. *Phillips*, 415 F.3d at 1314 (“Differences among claims can also be a useful guide in

understanding the meaning of particular claim terms.”). Specifically, claim 5 of the ’221 patent uses the transitional term “at least” to express a claimed amount *without* an upper limit. Thus, if Guardant had intended that the numeric range recited in claim 3 of the ’221 patent and claim 19 of the ’306 patent merely constituted a minimal floor (as Plaintiffs incorrectly contend), then Guardant certainly knew how to claim that. But Guardant did not, and instead used the word “between,” making it explicit that the claims cover a specified range.

(c) Plaintiffs’ Reply Position

Contrary to Guardant’s arguments, “comprises” is no less open-ended just because the claim language also recites a numerical range. In *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1366 (Fed. Cir. 2003), the asserted claim recited a process for producing *E. coli* cells “comprising” the step of growing the cells “at a temperature of 18°C. to 32°C.” The Federal Circuit observed that “comprising” in the claim “indicate[d] that the claim [wa]s open-ended,” and therefore allowed for growing *E. coli* cells outside the claimed range. *Id.* at 1369. The same, straightforward reasoning applies here.

The main case Guardant cites for support—*Jeneric/Pentron, Inc. v. Dillon Co.*, 205 F.3d 1377 (Fed. Cir. 2000)—is inapposite for at least two reasons. First, in *Jeneric*, the argument that “comprising” modifies a numerical range was not before the Court. *Dow Chem. Co. v. NOVA Chemicals Corp. (Canada)*, 629 F. Supp. 2d 397, 408 (D. Del. 2009) (“[The Federal Circuit] was not directly addressing the construction of ‘comprising’ [in *Jeneric*].”). Rather, the Court considered a composition claim using “comprising” to claim a weight percentage range of several ingredients. The Court found that construing the weight percentage ranges as encompassing anything more than the recited range would have vitiated the weight percentage ranges for other elements. *Jeneric/Pentron* at 1381. The claims in question here are entirely different; and “comprising” modifies a parameter for a *single* claim element, cfDNA. Second, the

Federal Circuit rejected the plaintiff's claim construction because the plaintiff had "rel[ied] on the precise ranges of the claims to distinguish itself from prior art during prosecution" and could not "later construe th[ose] ranges more broadly during an infringement action." *Id.* at 1382.

Guardant points to no similar evidence here.

Guardant's remaining cases are not on-point. The claims in *Ideal Instruments, Inc. v. Rivard Instruments, Inc.*, 498 F. Supp. 2d 1131, 1159 (N.D. Iowa 2007), like in *Jeneric*, dealt with weight percentage ranges of several elements. And *Wisconsin Alumni Research Found v. Apple Inc.* and *Spectrum Intern., Inc. v. Sterilite Corp.* are even further afield. Neither case involved the construction of claimed numerical ranges at all. *See generally Wis. Alumni*, 905 F.3d 1341, 1345-48 (Fed. Cir. 2018); *Spectrum*, 164 F.3d 1372, at 1379-80. (Fed. Cir. 1998).

Further, Guardant hurts, not helps, its position by pointing out these claims lack an "about" qualifier. Patentees typically use this term so they can claim a *closed* value range but with slightly expanded endpoints to account for margins of error. *See Takeda Pharm. Co. Ltd. v. Zydus Pharms. USA, Inc.*, 743 F.3d 1359, 1365 (Fed. Cir. 2014). That Guardant omitted this word only reinforces the conclusion that it never intended the claim to be a closed range.

Further, Guardant's claim differentiation argument fails. Claim 5 of the '221 patent uses "at least" and not "comprising." *See Vehicular Techs. Corp.*, 212 F.3d at 1383 (interpreting "comprising" to mean "I claim *at least* what follows and potentially more.") (emphasis added).

Indeed, if Guardant truly meant to claim "1 nanogram (ng) and 100 ng of cfDNA molecules" and nothing more, it would have led with "consists of." *See id.* ("a drafter uses the phrase 'consisting of' to mean 'I claim what follows and nothing else.' A drafter uses the term 'comprising' to mean 'I claim at least what follows and potentially more.'"). Guardant did not.

(d) Defendant’s Sur-Reply Position

The term “comprising” does not abrogate precise numerical ranges of a claim. *Jeneric/Pentron*, 205 F. 3d at 1381; *see also Spectrum Int’l.*, 164 F.3d at 1380 (“‘Comprising’ is not a weasel word with which to abrogate claim limitations.”). It is irrelevant that the Guardant claims have a single claim element after “comprising” rather than several elements following “comprising,” as in *Jeneric/Pentron*. Plaintiffs mischaracterize *Invitrogen Corp. v. Biocrest Mfg. L.P.*, 327 F. 3d 1364, 1341 (Fed. Cir. 2003), in which the Federal Circuit did not construe the claim to include growth *outside* the specified temperature range, and disregard *Wis. Alum.*, 905 F.3d 1341.

Guardant’s claims do not use the term “about.” A claim including a numerical range without the term “about” or other indicator of imprecision is limited to that precise range, *even when qualified by “comprises”*. *Takeda Pharm. Co. Ltd. v. Zydus Pharms. USA Inc.*, 743 F.3d 1359, 1364 (Fed. Cir. 2014) (emphasis added). And Plaintiffs’ proposed replacement of “comprising” with “consists of” would preclude the inclusion of elements other than cfDNA molecules. *Vehicular Techs. Corp. v. Titan Wheel Int’l, Inc.*, 212 F.3d 1377, 1382-3 (Fed. Cir. 2000). There is no support to rewrite this term in this fashion.

IV. Conclusion

A. Plaintiffs’ Conclusion

Plaintiffs respectfully request that the Court adopt their constructions.

B. Defendant’s Conclusion

Guardant’s proposed constructions should be adopted and the identified TwinStrand claim terms be found indefinite.

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